The Journal of Allergy

VOL. 23 SEPTEMBER, 1952 No. 5

Original Articles

A SUGGESTED QUANTITATIVE EVALUATION OF THE DEGREE OF SENSITIVITY OF PATIENTS WITH RAGWEED POLLINOSIS

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PROGRESS in the study of the therapy of allergy and changes in allergic status due to other causes has been hampered by the uncertainties of the usual subjective and objective measurements. It is true that ventilatory changes produced by asthma have been demonstrated.[1, 2, 3] The maximum breathing capacity (m.b.c.), perhaps combined with vital capacity (v.c.) readings, gives considerable information about the presence or absence of bronchiolar constriction during an acute episode or experiment or over any extended time interval. But the bronchi are subject to numerous specific and nonspecific influences, and without controlling the allergenic cause a ventilatory determination at any one moment may be totally misleading. Neither the titer of the skin test response, the reaginic titer nor the amount of neutralizing antibody[4] has any direct bearing on the severity of the clinical allergy or the therapeutic result from desensitization, ACTH, or cortisone.

It would seem reasonable, however, to presume that a diminution of symptoms referable to the respiratory tract would signify a lessened reactivity of the particular shock organ which should be demonstrable quantitatively. Attempts at testing the shock organ are by no means new. Blackley[5] inhaled grass pollen to prove the etiology of his hay fever. Dunbar[6] produced coryza by the application of pollen to the conjunctiva. Later, Noon and Cantab,[7] using dilutions of grass pollen, followed the decrease in conjunctival sensitivity during a series of injections of grass extract. Duke[8] suggested the application of substances to the ophthalmic and nasal mucosas as a diagnostic aid. He speculated on the idea that an inhalation test might be used to determine the cause of asthma. Vistreich, in a discussion of Blumstein's[9] paper on nasal tests in diagnosis, suggested tests with serial dilutions of pollen solutions to prevent overdosage and to estimate sensitivity. Flamm, in the same

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This investigation was supported, in part, by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service and the Upjohn Company, Kalamazoo, Mich.

Presented at the Eighth Annual Meeting of the American Academy of Allergy, Chicago, Ill., Feb. 18 to 20, 1952.

Received for publication, April 7, 1952.

*This work was done as partial fulfillment of the requirements for the M.S. degree.

discussion, proposed diluting the pollen with talc. Tuft and Blumstein[10] used dry pollen diluted with an inert powder to determine the sensitivity of the nasal mucosa and to follow the course of clinical improvement from desensitizing injections. Stevens[11] used atomized extracts of various inhalants as a diagnostic measure, but abandoned the procedure after encountering delayed, severe asthmatic reactions lasting up to several days. All of these investigators found that normal subjects tolerated the largest doses given without developing typical hay fever or asthma.

The need for some quantitative assay became apparent in the investigation of the therapeutic effect of various procedures on hay fever and asthma. After a number of preliminary variations the following technique was adopted for the present.

METHOD

Antigen Titrations.—The present study is concerned only with ragweed extract in ragweed-sensitive patients. Undoubtedly, however, any inhalant substance could be used in a similar manner. Throughout the course of this investigation we employed the same lyophilized preparation of equal parts of giant and short ragweed extract. Prior to its use the 3 per cent lyophilized extract was redissolved in one-third of its original volume of saline (with phenol), thus making it a 9 per cent solution. Ten dilutions were prepared, ranging from 300 to 90,000 pollen (Noon) units per ml. The same solutions were used for all determinations of mucous membrane and skin sensitivities.

TABLE I

SOLUTION NUMBER	NUMBER OF POLLEN UNITS PER ML.
1	90,000
2	60,000
3	30,000 (1:33 or 3%)
4	20,000
5	10,000
6	5,000
7	3,000
8	1,000
9	500
10	300

Starting with Solution 10, a drop was placed in the inferior conjunctival sac. Every five minutes the concentration was increased until a reaction, consisting of itching, burning, and redness occurred. When this level was established the conjunctiva was flushed with normal saline containing 1:400 epinephrine. The opposite eye was used for control and comparison, and was either left untouched or was tested with the diluent.

Since nasolacrimal drainage often caused a reaction in the homolateral nostril, the nostril tested was on the opposite side from the eye subjected to the test. A spray of the extract was administered by seven compressions of the bulb of a DeVilbiss plastic nasal atomizer. The average delivery was 0.014 ml. with a range of 15 per cent variation. To minimize the inhalation of the spray into the bronchi the patient held his breath during the nasal adminis-

tration and at the completion of the spraying sniffed gently. Every five minutes the concentration was increased until a reaction was obtained, consisting of one or more of the following symptoms: itching, rhinorrhea, sneezing, and nasal blocking. The reaction was usually arrested by a spray of Pyribenzamine solution, with the addition of a 1:4000 epinephrine solution if necessary.

The bronchial tests were made with an aerosol obtained from a Vaponephrin nebulizer with a hand bulb. With care and practice a fairly constant rate of delivery of aerosol could be obtained from the ten bulb compressions used for each administration. The average delivery on each administration was 0.021 ml. with a variation of 8 per cent. A positive reaction occurred in one to three minutes and took various forms: oppression or tightness in the chest, wheezing, cough, or dyspnea. The attack of asthma thus precipitated was terminated, often only temporarily, by the inhalation of epinephrine or the use of some other sympathomimetic compound. Several hay fever patients who had no history of previous asthma developed a cough, itching of the throat, or chest discomfort, often severe, from strong concentrations of the extract; however, ventilation tests revealed little or no bronchiolar constriction. The production of pulmonary symptoms accompanied by significant diminution in the m.b.c. was taken as the end point for bronchial titration.

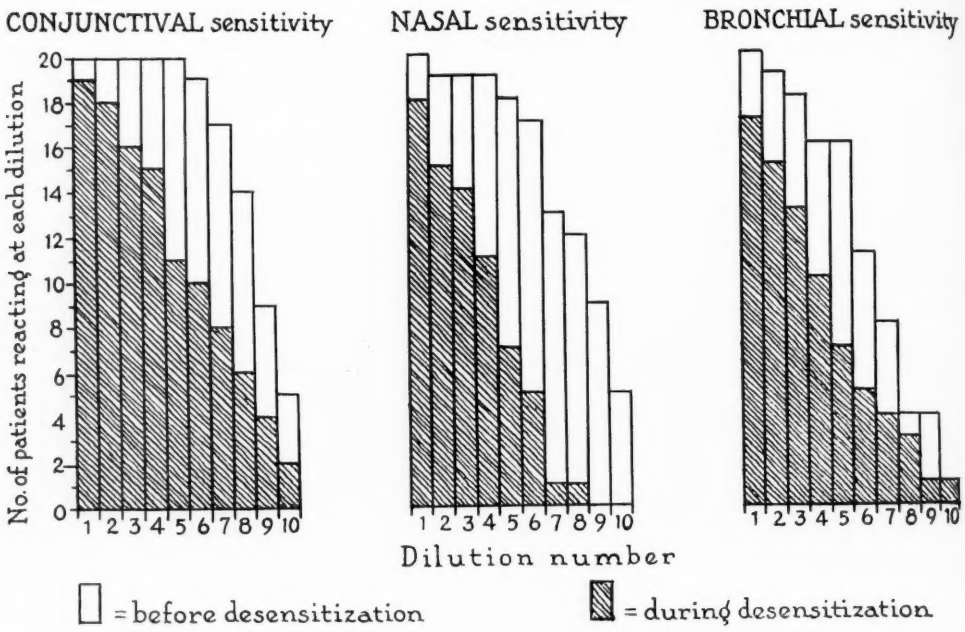
Ventilatory Function.—The vital capacity (v.c.) and maximum breathing capacity (m.b.c.) were determined at the beginning and at the completion of each set of mucous membrane titrations. The equipment consists of a rubber mouth piece, an inspiratory and expiratory high-velocity valve system, a Douglas bag, and a pocket-sized aneroid spirometer. This instrument has been shown by Cohen[12] to compare favorably in accuracy to the water bell type of spirometer. The vital capacity was determined at the beginning of the test period. While in the standing position, after a full inspiration, the patient exhaled completely into the spirometer. The best effort of at least three was recorded. Between administrations of bronchial test doses the v.c. was determined in order to detect any bronchial changes, according to the suggestions of Lowell and Schiller.[13] After pulmonary symptoms were produced the best of at least three efforts was recorded.

Determination of the m.b.c., as has been pointed out by others,[14] requires training of the subject. New patients were given adequate instruction, and then were shown the tests made on trained patients. Finally, after several short trials to get the feel, the test was performed. Since asthma attacks can be precipitated by this procedure, the test period was shortened from thirty to fifteen seconds. We found that the subject would select too shallow and rapid a level for maximum results if allowed to set his own volume. Consequently, the patient was instructed to make each breath about twice his tidal volume and to move this volume in and out as rapidly as possible. The timing was begun at the onset of the first expiration and the air was collected in the Douglas bag. The subject was encouraged and urged on during the test. At the end of fifteen seconds the bag was pinched shut and then emptied through the spirometer. This value miltiplied by four gave the m.b.c.

At least twenty minutes must elapse between each performance of the test, otherwise fatigue plus alkalosis due to hyperventilation will diminish the effort expended by the patient. The best of several attempts was recorded at the beginning of the procedure and at the time when pulmonary symptoms had been induced.

RESULTS

This study is based on forty patients who underwent the testing procedure one or more times. There were twelve subjects whose symptoms consisted of hay fever only. Twenty-eight patients suffered from varying degrees of hay fever and asthma during the ragweed season. These 40 patients were evenly divided between those who had never had desensitization therapy or whose treatment was not over twelve months long in the aggregate and those who had had at least a year or more of intensive therapy. To illustrate the application of this method only one phase of the results is considered at this time.



EFFECT of DESENSITIZATION in RAGWEED POLLINOSIS PATIENTS

Fig. 1.

Fig. 1 shows the effect of desensitization upon the mucous membrane sensitivity. The 20 untreated patients were compared as a group with the 20 who had received desensitization therapy. Patients have not yet been followed long enough to compare the changes in the readings of individual subjects as a result of hyposensitization. In the treated group there was a definite decrease in the number of patients reacting at each dilution. This decrease was somewhat more marked in the titration of nasal sensitivity. Some patients in the treated group failed to react to two administrations of the most concentrated extract but none of these failed to react in more than one site tested.

The number of patients examined by this procedure is as yet too small to justify a more detailed presentation. However, certain trends have become manifest. There seems to be an indication that a shock organ specificity exists. The hay fever patients, while reacting to high dilutions in the nose, tolerate strong concentrations of extract by aerosol before developing symptoms. So far no hay fever patient without a history of asthma has reacted to an aerosol of a dilution weaker than number 6. The asthmatic patients react to much higher dilutions of aerosolized extract. Several asthmatic persons have been encountered, who tolerate strong solutions in the nose but are very sensitive to the inhaled aerosols.

Considerable variability from one titration to the next was encountered in some patients. Others were fairly consistent in their reaction levels when tested before or well after the ragweed season. Twelve patients who had no complicating sensitivities were repeatedly tested out of season with ragweed pollen extract and fairly consistent results were obtained. Out of a total of 96 determinations of mucosal sensitivity only eleven individual tests varied as much as two dilutions:

TABLE I

M. S.	*Eye*	9,	9,	9,	9;	*Nose*	10, 8, 10, 8;	*Bronchi* 5, 6, 5
E. W.	*Eye*	9,	10,	10,	10;	*Nose*	10, 10, 9, 10;	*Bronchi* 7, 8, 8
L. L.	*Eye*	10,	8,	8;		*Nose*	10, 8, 10;	*Bronchi* 9, 8, 9
H. E.	*Eye*	9,	7;			*Nose*	7, 9;	*Bronchi* 7, 7
R. H.	*Eye*	9,	8,	8;		*Nose*	3, 4, 4;	*Bronchi* 7, 6, 6
L. Van O.	*Eye*	10,	10;			*Nose*	8, 8;	*Bronchi* 6, 6
G. S.	*Eye*	5,	7;			*Nose*	1, 1;	*Bronchi* 2, 3
J. K.	*Eye*	8,	8,	7;		*Nose*	5, 5, 6;	*Bronchi* 2, 2, 2
B. R.	*Eye*	7,	8,	8;		*Nose*	8, 7, 8;	*Bronchi* 4, 4, 5
J. J.	*Eye*	8,	7;			*Nose*	3, 3;	*Bronchi* 0, 0
A. D.	*Eye*	10,	10;			*Nose*	5, 5;	*Bronchi* 9, 8
F. S.	*Eye*	7,	7,	7;		*Nose*	8, 6, 8;	*Bronchi* 6, 6, 6

A number of other patients tested repeatedly showed considerable variability. In many instances an unexpected high sensitivity could be explained by the presence of a high count of atmospheric grass pollen or mold spores and the fact that the patient was known to be sensitive to these antigens. One patient was consistent for three titrations until the winter when her sensitivity greatly increased. She was markedly sensitive to house dust and apparently had been having rhinitis from it. Another patient was tested shortly after a bout of infectious bronchitis and found to have a markedly increased bronchial sensitivity.

DISCUSSION

The level of reactivity of the mucosas of the eyes, nose, and bronchi of 40 patients is reported to illustrate the method. Generally, conjunctival reactions occurred in a larger per cent of patients than did nasal or bronchial reactions. The eyes are probably not more sensitive than either the nose or bronchi but with our technique received a greater dosage per unit of surface. It would appear that the conjunctival sensitivity could serve as a reference point for comparison of nasal and bronchial reactions and in a general manner reflects the over-all sensitivity of the contiguous respiratory mucosa. Thus, it seems

that earlier workers utilizing the conjunctiva for diagnostic and therapeutic testing[6, 7, 15] may have had a valid basis for the estimation of clinical sensitivity. There also appears to be a correlation of the relative titer of sensitivity of each organ with the primary clinical picture of the patient. The hay fever sufferers manifest a high nasal sensitivity with low bronchial reactivity. The asthmatic patients have a high bronchial sensitivity with variable but generally high nasal sensitivity. This supports the clinical impression that the syndromes recognized as hay fever and asthma are determined at least in one respect by a difference in the relative sensitivity of the two "shock organs," the nasal and bronchial mucosa.

On the administration of strong concentrations of pollen extract the hay fever patient developed symptoms of cough, itching, and chest discomfort which often were quite troublesome, yet the m.b.c. was little if any diminished; whereas the act of extreme inspiration was accompanied by such distress and urge to cough that the v.c. was considerably diminished. Such a vital capacity determination cannot, however, be regarded as a true indication of the functional capacity of the lungs.

A phenomenon noted some time ago by Stevens[11] was encountered here also. After the bronchial symptoms were produced, patients were given an aerosol of some sympathomimetic agent for relief. Many also were given moderate doses of antihistamines to take during the next 12-24 hours. Nevertheless, several patients reported that upon retiring that night they noted a mild recurrence of the asthma. This symptom at times would occur for three or four subsequent evenings.

If such a "shock organ" specificity exists, it conceivably could involve any general region of the respiratory mucosa aside from the nasal and bronchial regions. We did find apparent tracheal and perhaps pharyngeal reactions in some patients. The sensations experienced at that time duplicated the patients' subjective experience during the season. These people did not manifest bronchoconstriction, so apparently the bronchi were not involved. Similarly the conjunctival mucosa could become a primary shock organ and perhaps such a condition exists in seasonal catarrhal conjunctivitis. However, the group tested did not include such a patient.

Of the 40 patients examined, 20 were untreated (or had minimal treatment) and 20 had had over a year of perennial desensitization. The general level of reactivity was definitely decreased in the treated group. The decrease in the level of nasal reactivity after treatment somewhat exceeds the decrease in the bronchial sensitivity. This might suggest that asthmatic symptoms are more difficult to control by desensitization than are hay fever symptoms. The experience of allergists is to the contrary. Several possibilities suggest themselves to explain this apparent discrepancy. The treated asthmatic patients included several subjects who had much higher bronchial than nasal sensitivity. Their bronchi then were the primary shock organ. These cases would weight the results in the treated group. It is also possible that naso-tracheo-bronchial

leakage had added to the dose of extract reaching the bronchi by aerosol. We are at present administering the bronchial aerosol before the nasal spray in order to evaluate this factor as a possible source of error.

As experienced by Tuft and Blumstein,[10] we found considerable variation from titration to titration on individual patients. It is our impression that this variability is not a fault of the method but rather reflects the shifting reactivity of the respiratory mucosa in response to numerous and diverse factors. If grass pollen or mold spores were present in the air, patients sensitive to mold, grass, and ragweed pollen would require less ragweed extract to produce a reaction, even though at the time of the titration they were symptom-free. The presence of infection or other disease of the respiratory tract may lessen the amount of extract necessary to produce symptoms. By use of a room in which the amount of pollen in the air could be controlled, Holmes, Treuting, and Wolff[16] demonstrated the influence that the emotional status and life situation have upon the threshold of mucosal reactivity. The variability present in these mucosal titrations reflects then the additive insult necessary to bring mucosal changes to their symptomatic threshold. Thus the greatest value of these titrations is not so much their absolute titers but rather in the changes they undergo in response to varying situations.

Many applications of this technique suggest themselves. Among these are the evaluation of the relative efficacy of various modifications of desensitization therapy, the determination of a level at which it is safe to discontinue treatment, the influence of drugs, and the effect of stress, emotion, pregnancy, and other nonspecific factors. Some of these studies are already under way, but more data and time will be required to arrive at any opinions. In a paper to be published[17] our results with this technique in patients treated with cortisone will be described. This procedure is applicable to the use of any inhalant, and the results with other causative agents might prove informative, especially with respect to the effect of one factor upon the patient's response to another.

SUMMARY

1. A quantitative method is presented whereby the response of the eye, nose, and bronchi to a specific antigen can be determined.

2. Twenty patients with ragweed pollinosis without desensitization therapy showed a greater sensitivity than that found in another group of 20 ragweed sensitive patients who had had more than one year of such treatment.

3. There was correlation between the history of clinical symptoms in a particular shock organ and the degree of sensitivity as shown by quantitative tests in the various tissues.

4. The methods, or future modifications of it, should be applicable to the study of various factors. Among these are variations in procedures in desensitization therapy, modified allergens, the effect of various nonspecific factors and nonspecific therapy and the establishment of safe levels at which to discontinue treatment.

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CORTISONE IN THE TREATMENT OF PATIENTS WITH RAGWEED POLLINOSIS. DETERMINATION OF CHANGES IN SENSITIVITY OF THE MUCOSA PRODUCED BY PRE- AND CO-SEASONAL CORTISONE ADMINISTRATION

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THE clinical improvement of some allergic diseases during the use of cortisone can be questioned no longer. However, it has not been sufficiently established by objective measurements that cortisone increases tolerance to allergens. It has been shown[1, 2] that the quantitative skin reaction to the specific allergen or to histamine remains unaltered. The primary object of the present investigation was to study the effect of cortisone on the reactivity of the shock organs to the specific allergen. Rose and associates[3] and Grob and associates[4] found that ACTH increased the tolerance of patients to inhaled allergens. In a previous paper, Feinberg, Stier, and Grater[5] described a method using ragweed extract in a series of dilutions to determine quantitatively the sensitivity of the conjunctival, nasal, and bronchial mucosas. Using this procedure, observations were made on the changes in the level of sensitivity of the mucosa produced by cortisone given out of season and during the ragweed pollinating seasons.

METHOD

Fourteen patients were selected, ranging from 13 to 61 years of age, giving a history of hay fever or asthma during August and September, and showing a positive skin test to ragweed pollen extract. None of this group had diabetes, tuberculosis, infections, or hypertension. One patient gave a history of an episode of hypertension after bilateral oophorectomy but had a high normal blood pressure on examination. Four patients had hay fever and 10 had both asthma and hay fever. Six had been undergoing desensitization therapy for periods varying from eleven months to fourteen years; 8 either had never had injections or had taken treatment for less than six months. In all but one patient, treatment was discontinued in the spring of the year. Since 2 asthmatic patients dropped out shortly before the ragweed season, 2 substitute asthmatic patients were selected for seasonal treatment.

Increasing concentrations of ragweed extract ranging from 300 to 90,000 pollen units (Noon) per milliliter (p.u.) were used for all tests. The test dose was delivered as one drop to the conjunctiva, the spray from seven compres-

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This investigation was supported, in part, by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service and Ciba Pharmaceuticals, Inc., Summit, New Jersey.

Presented at the Eighth Annual Meeting of the American Academy of Allergy, Chicago, Illinois, February 18-20, 1952.

Received for publication, April 14, 1952.

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sions of the bulb of a DeVilbiss No. 33 nasal atomizer to the nasal mucosa and the aerosol from ten compressions of the bulb of a Vaponephrin nebulizer by inhalation. The end points were as follows: for the conjunctiva—itching, burning, and redness; for the nasal mucosa—itching, rhinorrhea, and nasal blocking; for the bronchi—cough, wheezing, or dyspnea, accompanied by significant diminution in the maximum breathing capacity (m.b.c.). Each patient had at least one determination of mucosal sensitivity before the season and before any medication was given and 12 patients had two or more such base line studies. During administration of the hormone the level of sensitivity was determined once or twice a week. The mucosal sensitivity titrations were carried out between two and four hours after the morning dose of medication.

The weight, blood pressure, urinalysis, number of circulating eosinophils, and general condition of the patient were determined at least twice a week. Supervision of ventilatory tests and the determination of end points were always done by one individual (R. A. S.). The pollen extracts were always administered by the same person (M. W.) and the sensitivity levels obtained in each determination were not known to the other, until the end of each period. The results of each titration period were filed separately and not assembled until the period of hormone administration was over.

During the spring of the year each patient initially received a seven day course of oral cortisone,* consisting of 100 mg. daily, given in four doses of 25 mg. each. If no increase of pollen tolerance was manifest in one week, the same dose of cortisone was either continued or increased for another week. A significant increase in tolerance was obtained in 5 patients receiving 100 mg. daily for seven days, 6 for fourteen days, and 1 for twenty-one days. Two patients showed a fall in sensitivity only after 200 mg. daily for seven days, having previously shown no change after the seventh and fourteenth day with 100 mg. daily.

At the onset of the pollen season, the patients were allowed to develop symptoms for several days before starting cortisone orally. Most patients began taking the drug August 21 to 23. Three began on August 28 and 3 on August 30. If symptoms persisted after two or three days the dosage was increased. As soon as two or three days had elapsed without symptoms the dosage was decreased. Thereafter, the minimal dosage of cortisone was used to maintain the patients with minimal symptoms. The first estimation of mucosal sensitivity was made while the patient was on the maximum dosage of cortisone. Subsequent estimations usually were made after the subject's medication had been decreased.

An attempt was made to determine the effect of cortisone on the absorption from the connective tissue[6, 7] by estimating the time of disappearance of intracutaneous wheals produced by 0.2 ml. of various saline solutions consisting of histamine, histamine plus hyaluronidase, hyaluronidase in concentrations varying from 200 to 10 turbidity reducing units per ml., and saline solu-

*Cortone by Merck.

tion. The histamine used was a 1:1,500 dilution calculated as the free base. Initially fluorescein was incorporated in the solutions and the time for disappearance of fluorescence was estimated using a Wood's lamp. However, it was observed that fluorescin absorption did not parallel the fluid absorption. Thereafter, the end point was taken as the time when the skin over the injection site, when pinched up between the fingers, was no longer palpably thicker than the uninjected skin over the same area of the opposite forearm.

RESULTS

Clinical.—All of the patients obtained considerable relief under cortisone therapy. Asthmatic symptoms were more readily relieved than were hay fever symptoms. Table I indicates the effect of maximum doses of cortisone on the symptoms.

TABLE I

	HAY FEVER SYMPTOMS	ASTHMA SYMPTOMS
No relief	0	0
Partial relief	10	2
Complete relief	4	8

Six patients completely relieved of their asthma continued to have minimal to moderate hay fever. Of the four patients having hay fever symptoms only one obtained complete relief on 100 mg. daily; the others required 150, 200, and 200 mg. daily, respectively, and obtained only incomplete relief. One asthmatic patient obtained relief from asthma on 300 mg. daily but moderate rhinitis continued. Another asthmatic patient had incomplete relief of both hay fever and asthmatic symptoms on 100 mg. daily and probably received an inadequate dosage. The third asthmatic patient was incompletely relieved on 200 mg. daily and continued to be awakened each morning by mild asthma. His hay fever was promptly relieved by cortisone and did not recur. His was the longest period of treatment, 71 days, as well as the largest total dosage, 6.6 Gm., due to the marked postseasonal prolongation of asthmatic symptoms.

All patients required 100 mg. or more of cortisone daily to obtain their initial maximum relief. Four required 100 mg., one 150 mg., eight 200 mg., and one 300 mg. daily. The duration of treatment varied from eight to seventy-one days with 12 patients treated from thirteen to thirty-one days. The total cortisone dosage varied from 700 mg. to 6,600 mg. Ten patients received 2,200 to 2,875 mg. of the hormone.

Abrupt discontinuance of cortisone in the latter part of the season precipitated severe recurrence of rhinitis, often within six to eight hours and always within twenty-four hours. Asthmatic symptoms usually returned within twenty-four hours but were delayed two or three days in some cases. In contradistinction gradually decreasing doses over a period of ten to fourteen days tided the patients over the declining days of the season without any exacerbations upon cessation of hormone therapy. Late in the season some patients reported that moderate morning or evening symptoms were relieved

by 25 to 50 mg. of cortisone. However, since such symptoms are usually temporary and resolve spontaneously, it is doubtful whether these infrequent small doses were effective.

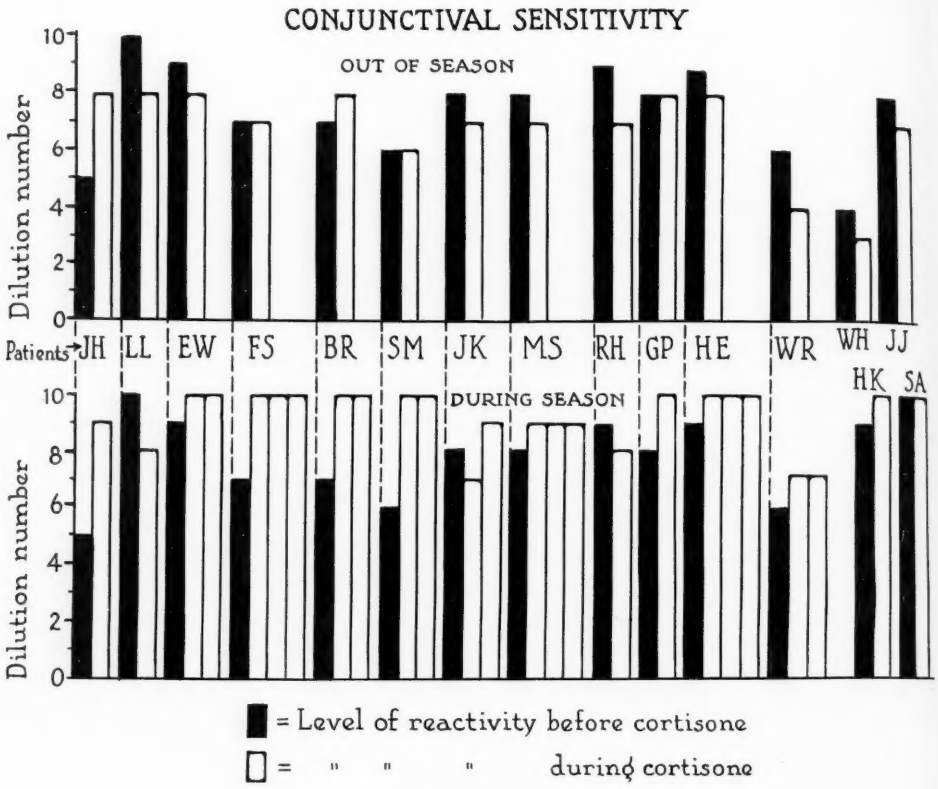

Fig. 1.

Figs. 1, 2, and 3.—Each graph represents the reactivity of the conjunctiva, nose or bronchi in individual patients before and after cortisone therapy. The height of a column designates the weakest dilution producing a response. The numbers indicate the strength of the solution, the weakest dilution being No. 10. The dark column is the level of reactivity before cortisone, the light after cortisone. The upper portion of each graph shows the values obtained when cortisone was administered out of season. The light columns in the lower portion of each graph indicate the values obtained after cortisone was administered during the hay fever season.

A high incidence of unpleasant side reactions was encountered. Ten or 71 per cent of the patients developed untoward symptoms that cleared when the hormone was discontinued or drastically reduced. Of these, individual minor complications were: insomnia, 5; transient glycosuria (with a blood sugar under 100 mg. per cent), 3; dysuria and polyuria, 2; rounding of the face, 1; headache, 1; nausea, 1; ankle edema, 1; and acne, 1.

The minor reactions that occurred in 8 (57 per cent) of the cases were present during maximum dosages of hormone and cleared up when the dosage was reduced. The insomnia began with euphoria, harder and longer periods of work, and inability to relax. The patients slept fitfully or not at all, even after taking barbiturates. In a few days they felt lethargic, worn out, and

depressed. Mild dysuria and polyuria in two women were not accounted for by abnormal findings in the urine and the symptoms cleared when the drug was decreased. Three patients experienced a gain of six to eleven pounds while on cortisone, but in each the weight gain was probably due to the voracious appetite. One of these patients had a transient ankle edema that disappeared while still on the hormone.

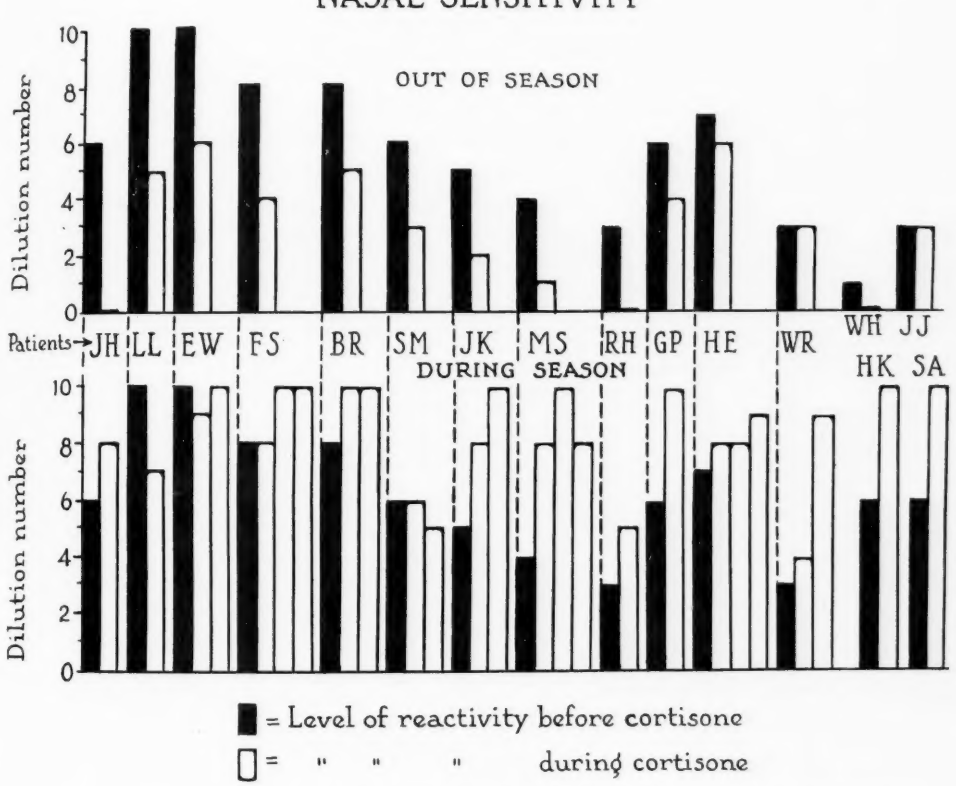

Fig. 2.—For explanation, see Fig. 1.

Three patients developed such major reactions that the hormone had to be discontinued. One 18-year-old girl, on 200 mg. of cortisone daily, developed acneform pustules, one of which on her forehead went on to marked inflammation. When seen after twenty-four hours there was a rapidly spreading edema of her forehead. She had no fever, erythema, or local heat but the upper cervical lymph nodes were markedly swollen and exquisitely tender. She was hospitalized and given antibiotics with recession of the swellings. Subsequently, she tolerated 100 mg. of cortisone daily with incomplete relief of the rhinitis.

A 30-year-old woman required 300 mg. of cortisone daily for relief of asthma. She did not sleep for two days and became extremely weak and depressed to the degree of psychosis. Two days after stopping the drug she had recovered from her depression but again had severe hay fever and asthma.

The third patient, a 37-year-old woman, had previously received estrogens for a transient hypertension after bilateral oophorectomy. The highest blood pressure recorded before the season and during preseasonal cortisone was 150/90. Partial relief of her hay fever was obtained with 200 mg. of cortisone daily but she developed insomnia followed by a severe headache with blurring vision. Her blood pressure rose to 208/136. The headache and insomnia disappeared when the cortisone was stopped, but a blood pressure of around 216/122 persisted until estrogens were given again.

Since these severe reactions occurred on the thirteenth or fourteenth day the dose of hormone given in the first fourteen days could be compared with that for the other patients. The first 2 patients discussed above received the highest doses given in this fourteen day period, 2235 and 2200 mg. The third patient received 1600 mg. and ranked seventh in the amount given.

TABLE II

POLLEN UNITS (NOON) MIXED RAGWEED EXTRACT PER MILLILITER	REFERENCE NUMBER ASSIGNED EACH DILUTION
90,000	1
60,000	2
30,000 (1:33)	3
20,000	4
10,000	5
5,000	6
3,000	7
1,000	8
500	9
300	10

Experimental Studies.—Table II lists the concentrations of the ragweed extract dilutions and the reference numbers used in Figs. 1 to 3. In the upper portion of graphs, Figs. 1, 2, and 3, the changes in mucosal reaction levels before and during cortisone out of season are charted for each patient. The least change occurred in the ophthalmic sensitivity. Ten patients showed changes of one dilution or none at all. Three showed a decrease in sensitivity of two dilutions and one an increase of three during cortisone therapy.

The nasal sensitivity revealed the greatest change, with a decrease of two to six dilutions in 10 patients. Two patients showed a decrease of one dilution, 2 were unchanged, and 3 patients showed no reaction of the nasal mucosa from two applications of the most concentrated extract.

The bronchial sensitivity was also decreased by cortisone. The 4 patients with uncomplicated hay fever showed no reaction to pollen extract weaker than dilution No. 2 (60,000 p.u.), and in 2 there was an abolition of the bronchial reaction to the strongest concentration during cortisone treatment. These were patients J. H., S. M., J. K., and M. S. Ten had a decrease of from one to four dilutions. One was unchanged and one increased one dilution in sensitivity.

In the lower portion of Figs. 1, 2, and 3 the mucosal reactions determined before the season and before cortisone treatment are compared with the levels of reaction at the point of maximum cortisone dosage during the season. In addition, 8 patients received one or two more tests while on lower cortisone dosages. In nearly every patient there was a moderately to markedly increased sensitivity of each shock organ. The only significant decrease, two dilutions in the ophthalmic reactivity and three dilutions in the nasal test, occurred in patient L.L. while on 300 mg. of cortisone daily. The 4 patients with uncomplicated hay fever showed a marked rise in the level at which symptoms of tightness in the chest and cough could be produced. Auscultation of the chest never revealed wheezing at this time and the m.b.c. was diminished very little if at all.

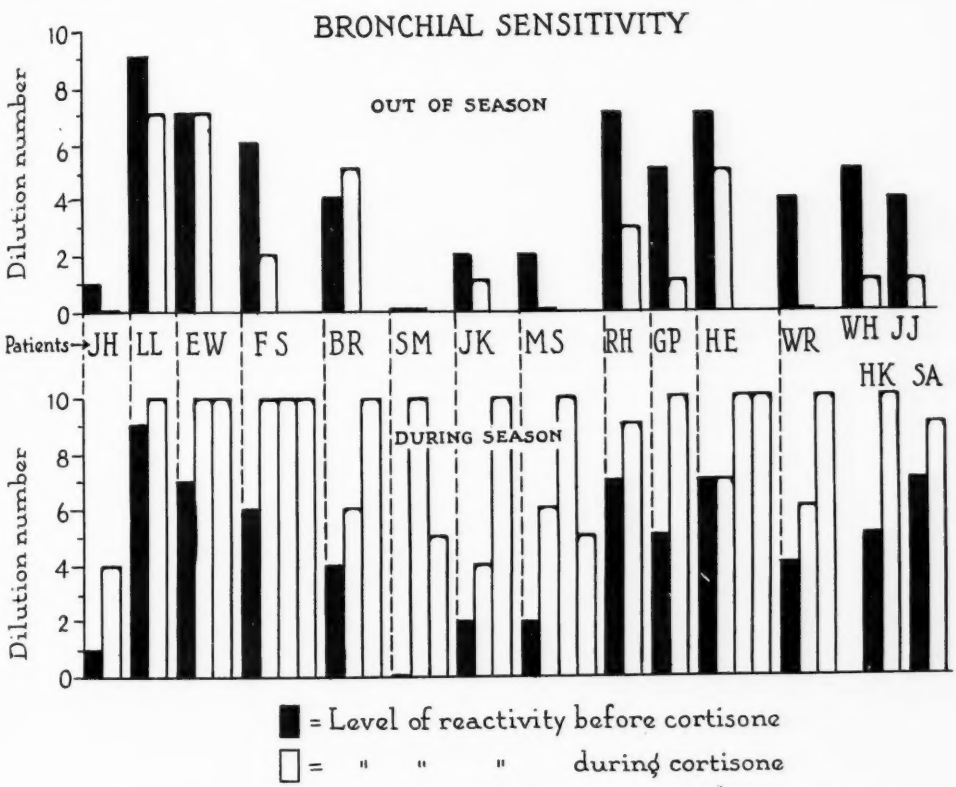

Fig. 3.—For explanation, see Fig. 1.

Patients needing the largest doses of cortisone to produce a decreased mucosal response before the season required 200 mg. a day or more of cortisone at the peak of the season. The best clinical relief was obtained in those patients showing the greatest decrease in sensitivity during preseasonal administration of cortisone. However, there was no significant correlation between the preseasonal dose and that required during the season.

During the preseasonal period of cortisone administration the level of circulating eosinophils was diminished by more than 50 per cent of the initial level in all but 3 patients. Nevertheless, these 3 patients showed a significant decrease in their mucosal sensitivity. With an increase in the dose of cortisone a further decrease in sensitivity occurred, but one patient still failed to show a fall in eosinophils. During the seasonal treatment with cortisone every patient showed a fall in eosinophils of over 50 per cent at the period of maximum dosage. There was no correlation between the degree of fall of eosinophils and the degree of symptomatic improvement. The first eosinophil determination after two days on a constant dose of cortisone was the lowest.

There was considerable variation in the time of absorption of fluid injected intracutaneously but in most instances a delay was observed. The wheals produced by normal saline disappeared in 15 to 120 minutes while on cortisone therapy, as compared to 13 to 85 minutes before treatment. The disappearance time of wheals produced by histamine before and during treatment paralleled but was somewhat longer than those for the normal saline—10 to 105 minutes before treatment and 16 to longer than 120 minutes during cortisone administration. The wheals from varying dilutions of hyaluronidase from 200 to 10 turbidity reducing units per ml. disappeared in half a minute to eighteen minutes with prolongation of the disappearance time during cortisone up to forty-five minutes; this was especially marked in concentrations below 50 units per ml. The skin underwent a different type of local reaction to hyaluronidase during cortisone administration. The erythema about the wheal was much more intense. Shortly after the swelling disappeared, it reappeared and persisted for an additional ten to thirty-five minutes longer. The phenomenon of recurrence was most marked at higher concentrations.

In 8 patients, reagin and thermostable antibody titers were determined before the ragweed season and shortly after the height of pollination while on cortisone therapy. There was considerable variation in the individual reagin titers, but no titer change was observed during treatment. Five patients had been receiving ragweed injections for over a year prior to May of 1951. Two of these, and one patient who had not received injections, showed thermostable antibody but no appreciable change in titer was detected during seasonal treatment with cortisone.

DISCUSSION

The therapeutic scheme of increasing the dose to parallel increasing symptoms and amounts of pollen in the air resulted in the largest dosage at the end of the first fourteen day period. It is possible that this scheme by favoring greater pituitary suppression, necessitated larger amounts for maximum effect than would be required if larger doses were used at the beginning of therapy. The increased amounts of hormone administered gave increased opportunity for the production of adverse reactions. Glycosuria without hyperglycemia appearing early in cortisone therapy and disappearing spontaneously was probably a result of increased glomerular filtration, as indicated by Earle and associates.[9]

Cortisone is not satisfactory as the sole treatment for most cases of seasonal allergy. Several patients requested a return to desensitization therapy in preference to suffering the same unpleasant reactions. The majority of patients felt they had experienced fewer hay fever symptoms with cortisone than they had had since developing their allergy. Although increasing and high cumulative doses are inadvisable, cortisone would seem to be of value for brief periods of time at the peak of the pollen season. Relief may be afforded those patients who obtain unsatisfactory results from desensitization therapy or who cannot reach sufficiently large doses of extract because of local or systemic reactions. The results of the titrations described suggest that cortisone exerts its effect most intensely on those tissues which constitute the specific shock organ rather than equally on all the mucous membranes. In other words, cortisone produces the greatest change where apparently the greatest abnormality exists. It is unlikely that cortisone should be selective in itself. Therefore, the alterations taking place in specifically sensitized tissues are reversible by the nonspecific ability of cortisone to alter the reactivity of all tissues.

An attempt was made to determine the mucosal sensitivity of the first 4 patients who presented themselves for cortisone treatment at the beginning of the ragweed pollinating season. A prompt and intense injection of the conjunctivas and paroxysms of sneezing or nasal blocking occurred in response to the greatest dilution of extract. After these exaggerated reactions all 4 patients declined to inhale the aerosol of the extract. Because of this experience, pretreatment assays during the season were abandoned. A study of the data comparing the sensitivity during the pollen season with that of the base line obtained before the season might lead one to conclude that cortisone caused no increase in tolerance. Actually cortisone increased the patient's tolerance sufficiently so that the airborne pollen produced only mild or no symptoms. This discrepancy between the results of the assays and clinical results is probably explained by the consideration that although cortisone diminishes the reactivity of the tissues to pollen, the dose to which the patient is exposed during the assay is the sum of the pollen applied artificially and that encountered naturally.

The patients with hay fever also showed a marked decrease in the tolerance of the bronchial mucosa during the pollen season. Symptoms were produced, often by the very dilute solutions, but there was little or no decrease in the m.b.c. The symptoms of cough and chest discomfort could have arisen from irritation of sensory nerve endings in the larynx, trachea, bronchi or bronchioles since apparently no diminution in the caliber of the bronchioles occurred. One patient with a history of a single stormy hay fever season consistently showed a slight decrease in m.b.c. during the season. The possibility of true asthmatic involvement is to be considered in this patient.

Asthmatic patients quite often would experience a recurrence of asthma about twelve hours after the estimation of bronchial sensitivity. Sometimes this would last for several days. Only a few patients on seasonal cortisone therapy noted transient and mild recurrences of chest tightness after the bronchial titration. It is known that patients suffering from pollinosis often

continue to have symptoms for some time after pollen disappears from the air. It is possible that seasonal cortisone therapy given such patients would decrease the severity of persistent bronchiolar changes.

The delay in the absorption of intracutaneously injected saline and of saline and histamine may indicate that cortisone impairs the absorbtive mechanism. The ability of hyaluronidase to increase diffusion in connective tissue was diminished by cortisone. A reappearance of swelling after disappearance of the wheal produced by hyaluronidase was unexpected but may have a plausible explanation. Cortisone, by delaying the diffusion of hyaluronidase, causes a local retention of the enzyme in a higher concentration. The effect is an alteration of the ground substance of the local blood vessels permitting engorgement and exudation of fluid which results in a local recurrence of swelling. The increased erythema which was noted indicates some changes in the vascular response.

The symptomatic and objective improvement brought about by cortisone was not associated with any change in the circulating reagin or the thermostable blocking antibody. These findings are in conformity with the observations of other workers.[1, 2, 10, 11]

SUMMARY

1. Fourteen patients having hay fever or a combination of hay fever and asthma due to ragweed were given oral cortisone. The hormone was administered for a short time several months before the ragweed season and again during the pollinating season. Changes in the mucous membrane sensitivity of the eye, nose, and bronchi were determined quantitatively during both periods.

2. Symptoms of hay fever were more difficult to control than were those of asthma.

3. Ten patients developed untoward reactions. Cortisone had to be discontinued in 3 patients because of severe complications. Reasons for this high rate of side reactions are suggested.

4. Cortisone given out of season decreased the sensitivity of the mucosa to ragweed extract. The greatest change occurred in the organs primarily affected.

5. After obtaining relief from cortisone administered during the pollinating season, a dilution of pollen weaker than that required prior to the season produced a reaction of the mucosa.

6. The time of disappearance of intracutaneously injected saline or histamine was somewhat lengthened by cortisone. The disappearance time of hyaluronidase was markedly prolonged. The altered reaction to hyaluronidase is discussed.

7. There was no detectable change in the titers of the skin sensitizing antibody or the thermostable antibody in the patients treated with cortisone.

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INCREASING CASTOR BEAN ALLERGY IN SOUTHERN CALIFORNIA DUE TO FERTILIZER

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IN 1923 Bernton[1] reported a case of asthma due to castor bean sensitivity in a laboratory worker. This man had been working with the beans on a research project. Since that time approximately fifty cases of allergy to the inhalation of castor bean dust have been reported in the literature. The work of Figley and Elrod[2] demonstrated that 30 out of 32 asthmatic persons who lived in close proximity to a castor oil factory were highly sensitive to an extract of the dust. This work was, I believe, significant in that it demonstrated an unusually high incidence of respiratory allergy in an area which was heavily contaminated with the fine dust particles of the castor bean. It suggests that sensitivity may be rather easily acquired through close association with this highly potent allergen. Vaughan[3] reported three cases of castor bean allergy in persons who were exposed to the castor bean pomace used in fertilizer. Robbins,[4] Arnold,[5] Snell,[6] Follweiler and Haley,[7] Barnard,[8] and Bennett and Schwartz[9] have all contributed to the literature of clinical allergy to castor bean dust. Ratner[10] who had previously succeeded in sensitizing guinea pigs by the inhalation route to other allergens stated that castor bean dust was a potent sensitizer by this same method.

During the last six years I have seen 17 patients who showed markedly positive skin reactions to a 1:10 crude extract of the castor bean by the puncture method. The puncture test consists of pricking the skin once with the sharply ground double point of the partially cut-off eye of an ordinary sewing needle, which has just been dipped into the solution of antigen. In 14 of these patients it has been possible to elicit a history of clinical sensitivity to the dust of the bean, and 11 have had either clinical hay fever or asthma from inhaling the pomace now being used commercially as fertilizer.

Serum was drawn from only 5 of the 14 clinically sensitive patients. Circulating reagin was demonstrated in all by passive transfer. The technique consisted of the intracutaneous injection of 0.1 c.c. of serum from each into a separate site on the forearm of the recipient. Forty-eight hours later each of the 5 sites was challenged by puncture testing each site with a 1.10 crude extract of the castor bean. Two control puncture tests were made with the same extract.

Ten of the 17 patients were tested both by the puncture and intradermal methods with extracts of the pollen of Ricinus communis (castor bean). These reactions were all negative.

Correlation between positive skin reactions and clinical sensitivity is at times difficult to clarify. Although scientific proof may be obtained by having the patient inhale the allergen in question under controlled conditions, I was not enthusiastic over this approach when dealing with a substance as potent as castor bean. I am, therefore, presenting brief case histories of this group of patients in support of my position.

Received for publication, April 4, 1952.

CASE HISTORIES

CASE 1.—E. B., a 57-year-old white, male, American, married, retired auditor. He was first seen in October of 1951 because of an asthma of 6 weeks duration.

In September of 1951 he spread approximately seven pounds of castor bean pomace on a small patch of dichondra (a grass substitute for lawns). While doing this job his nose and eyes began to itch and water, and he sneezed excessively. Very shortly thereafter his chest became tight and he retired to the house to sit down. His wife found him about a half hour later in great respiratory distress, sweating profusely, and cyanotic. The doctor whom she called immediately administered epinephrine, which gave only temporary relief. He was hospitalized for two days, but was still wheezing slightly when dismissed. During the next 6 weeks he continued to have asthmatic attacks in spite of home treatment with epinephrine, tedral, aminophylline, and finally a course of cortisone.

TABLE I. SUMMARY OF CASES

PATIENT	AGE	SEX	RACE	SKIN TEST REACTIONS	PASSIVE TRANSFER REACTIONS	CLINICAL FROM CASTOR BEAN	SOURCE OF MATERIAL
1. E. B.	57	M	W	++++	+++	Asthma	Fertilizer
2. J. D.	25	F	N	++++		Asthma	Fertilizer
3. V. L.	31	F	W	+++	+++	Cough	Fertilizer
4. A. B.	30	F	W	++++		Asthma	Ricinus communis Plants in neighborhood
5. M. R.	16	M	W	+++		Asthma	Fertilizer
6. M. H.	29	F	W	++++	+++	Asthma	Fertilizer
7. W. J.	24	F	W	++++		Asthma	Fertilizer
8. P. E.	6	M	W	++		Hay Fever	Fertilizer
9. J. T.	57	F	W	++++		Asthma	Fertilizer
10. C. A.	28	F	W	+++	++++	Asthma	Fertilizer
11. M. A.	57	F	Mongolian	+++	+++	Asthma	Fertilizer
12. R. S.	30	M	W	+++		Asthma	Fertilizer
13. C. G.	27	F	W	+++		Hay Fever	Ricinus communis Plants in neighborhood
14. E. L.	35	F	W	++++		Asthma	Castor bean dust
15. R. O.	7	F	W	++		Has Asthma; cannot correlate with castor bean sensitivity	
16. A. S.	29	F	W	++++		Eczema and Asthma; cannot correlate with castor bean sensitivity	
17. E. E.	14	F	W	++		Asthma. Never correlated with castor bean.	

I saw him in October of 1951 after approximately 6 weeks of chronic asthma. On physical examination the following essential points were noted: Blood pressure, 190/110; Dry tongue; moderate emphysema; dry fine expiratory wheezing râles throughout chest; no ankle edema; chest x-ray and ECG, normal.

Three days of hospitalization with intravenous fluids, iodides and aminophylline resulted in complete relief. The blood pressure dropped to 140/85. During his stay in the hospital all traces of the castor bean dust were removed from the home. The area of dichondra which had been fertilized was kept soaked for days. Since his return home he has been entirely well.

He was tested by the puncture method in my office to about 150 allergens and showed but one reaction—4 plus to castor bean.

It is of interest to note that in July of 1951, three months before the onset of his asthma, he fertilized his entire front lawn with about 100 pounds of castor bean pomace. During this process the only reaction was a runny nose. It is also of interest that he has never had asthma previous to the present episode.

CASE 2.—J. D., a 25-year-old, American, married, Negro housewife. She was first seen in 1950 because of asthma.

This woman was approximately 7 months pregnant and was doing well until her husband fertilized the front lawn with castor bean pomace. Within a half hour after he came into the house she was having a violent attack of asthma. An injection of ¼ c.c. of 1:1000 epinephrine controlled the attack. She was seen a few days later and tested to approximately 80 allergens. Castor bean showed a 4 plus reaction by puncture. All others were negative. This was her first and only attack of asthma in 15 years.

CASE 3.—V. L., a 31-year-old white, American housewife. She was first seen in 1950 because of a chronic cough.

This patient was a very interesting problem in that she was sent to me by a chest surgeon, to whom she had been referred with a diagnosis of possible bronchiectasis. The chest surgeon's history and physical examination suggested that the cough was of allergic origin. Complete skin tests, both puncture and intradermal, were done, and the only positive obtained was a 3 plus reaction by puncture to castor bean dust. Investigation disclosed that adjoining neighbors had been using the castor bean pomace on their lawns. Attention to the details of eliminating the dust has resulted in a complete cessation of the cough.

CASE 4.—A. B., a 30-year-old, white, American housewife. She was first seen in 1949 because of asthma.

Routine skin testing provided the key in detecting the cause of this woman's asthma. She had had some asthma in childhood, but had been entirely free for many years. Within a week after moving into a new home, approximately 6 months before I saw her, she had gone into status asthmaticus, which had required hospitalization. Upon her return home following this hospitalization she became chronically ill with asthma. History taking did not seem to give any clues, but when the skin tests were done there was a 4 plus reaction to the castor bean extract by the puncture method. Investigation of the home disclosed a large patch of *Ricinus communis* (castor bean) growing at the back of the lot, in close proximity to the clothesline. These plants were practically trees, some of them over 20 feet in height, and had obviously been there for many years. Removal of this group of plants and soaking down the back yard was only partially effective in the control of her disease. Eventually the entire inside of the house was scrubbed, the back yard was plowed up, soaked with water every day for 2 weeks, and the neighbors on each side of the house eliminated their castor bean plants. She gradually improved, and has had no severe asthmatic attacks since. This house was in a new tract and we were never able to determine whether castor bean fertilizer had been used on the new lawns.

CASE 5.—M. R., a 16-year-old white, American schoolboy. He was first seen in 1950 because of asthma.

This boy had been quite well until about a month before I saw him, at which time while playing with a friend on a neighbor's lawn he suddenly developed violent sneezing and itching of his nose. Asthma followed within a half hour. Adrenalin was administered at the Emergency Hospital. Following this episode he continued to have occasional mild spells of asthma, and came in for investigation. The skin tests disclosed a 3 plus puncture reaction to the castor bean extract, and investigation by the parents turned up the fact that the lawn on which he had been playing, when he had the first attack, had been fertilized with castor bean pomace approximately a week earlier. No further treatment seemed necessary and he has been well.

CASE 6.—M. H., a 29-year-old, white, American housewife. She was first seen in 1951 because of asthma.

She had not had any asthma for many years until on May 30, 1951, the lawn was fertilized with castor bean pomace. Within an hour or so after this process was started she had nasal symptoms and severe asthma. She went to the beach that night and the asthma cleared. On returning to the home the asthma recurred. She was referred to my office, and on complete skin testing there was a 4 plus reaction to castor bean by the puncture method, and no other significant reaction. She was advised to return to the beach temporarily.

A thorough house cleaning, during her absence, and constant soaking of the lawn have enabled her to live at home. She does, however, still have a little mild asthma, which is readily controlled by medication.

CASE 7.—W. J., a 24-year-old, white, American housewife. She was first seen in 1946 because of asthma.

Her mother died when the patient was 7, father remarried when she was 10, and about that time she began having asthma. After a period of adjustment the asthma disappeared completely. At the age of 23 the asthma recurred. She had been married 5 years and was the mother of 3 children. After about three violent attacks she was referred to me, and it was found on questioning that the most recent of these attacks had occurred following the spreading of castor bean pomace on their rather extensive lawns. Thorough soaking of the lawns over a period of many days, complete house cleaning, including walls and furniture, resulted in cessation of the asthma. Some weeks later her two small sons came into the house from play and were in close contact with her. Within minutes her nose began to itch, her eyes watered, and she began to wheeze. Superficial analysis might suggest a psychological problem here, but questioning disclosed that the two boys had been in the green house throwing handfuls of the castor bean fertilizer at each other, and their clothing was, of course, well saturated with the material. Careful attention to the removal of all castor bean fertilizer from the premises resulted in a complete cessation of the asthma. Complete skin testing by puncture and intradermal techniques disclosed a 4 plus puncture reaction to castor bean and questionable reactions to house dust and pyrethrum. These latter two were considered to be unimportant.

CASE 8.—P. E., a 6-year-old, white, American schoolboy. He was first seen in 1949 because of hay fever.

The patient eliminated contact with castor bean fertilizer by avoiding a certain neighbor's lawn, and the hay fever improved sufficiently so that no further treatment was needed. Puncture reaction to castor bean dust was 2 plus, questionable reaction to molds. No other sensitivities.

CASE 9.—J. T., a 57-year-old, white female, American teacher. She was first seen in 1951 because of hay fever and mild wheezing.

Approximately 6 weeks before I first saw her, she had a violent attack of hay fever with mild wheezing, following a fairly heavy exposure to castor bean pomace, used in fertilizing her garden. It is of interest that when she used to visit her parents in the Santa Ana area approximately 20 years ago she always had hay fever, and has noted since that wild castor beans grow in profusion around the place. For a number of years she has taught a course twice weekly at a plant nursery, and always has had some hay fever and cough at those times. Complete skin testing disclosed a 4 plus reaction to castor bean dust and 1 plus reaction to house dust. She is under treatment for the house dust and is much improved. She has been careful to avoid castor bean contact.

CASE 10.—C. A., a 28-year-old, white, American housewife. She was first seen in 1946 because of asthma.

When this young woman first came to me she was having chronic asthma. Complete skin tests at the time were negative, except for a 3 plus puncture reaction to castor bean. It seemed unlikely that this was the cause of the asthma. Investigation disclosed sinusitis and after this condition was cleared the asthma gradually became less of a problem. Because of the severity of the disease we attempted specific treatment with a castor bean extract. After four months this was discontinued, since it seemed to be ineffective. It is of interest to note that as a 10-year-old child she and some of her friends made "castor bean soup." Fortunately they ate very little of it, but even so she was violently ill with severe abdominal cramps for days. I was not able to obtain a clinical history of asthma as a result of exposure to castor bean dust until very recently. While driving by a church on her way home from my office she noted that the lawn of the church was being fertilized and the dust from this was blowing across the street. Within 5 minutes she was having hay fever, and by the time

she arrived home detected a definite wheeze in her chest. She telephoned the church and the gardener confirmed her suspicions that the fertilizer he was using was castor bean pomace. This attack was very mild and passed off rapidly.

CASE 11.—M. A., a 57-year-old widow, Japanese born, agricultural worker. She was first seen in 1951 because of asthma.

In the spring of 1951 this woman began having hay fever while working in a 3 acre strawberry patch. The strawberry beds were treated with castor bean pomace one afternoon while she was working there, and the hay fever became very severe. After her return home that evening her chest tightened up and during the night she had her first severe attack of asthma. I saw her early the following morning and there were the usual typical expiratory râles of a subsiding attack. Due to the fact that this woman spoke no English it was only later, after skin testing was done, that we learned the composition of the fertilizer which had been used on the strawberry patch. She had a 3 plus reaction by the puncture method to castor bean, and this was her sole skin sensitivity on complete testing. Her tolerance appears to be reasonably high, because she continues to work in the strawberry fields and avoids them now only during periods of fertilization. She recently had a mild attack of asthma after doing some work in her son's garage. He is a gardener and transports castor bean fertilizer in his truck. The family have now been alerted to the necessity of keeping her away from this allergen. It is of interest to note that during the war she was in a Japanese detention camp in Arizona, where there was a great deal of *Ricinus communis* growing.

CASE 12.—E. S., a 30-year-old, American, dairy delivery man. He was first seen in 1948 because of nasal allergy and occasional asthma.

This man came to my office because of nasal blockage, headaches, and nasal discharge. He was referred by a psychiatrist who had been treating a nervous condition which he developed in the South Pacific during the war. His sensitivities were mild to the chenapod group of pollens, house dust, and shell fish. Castor bean was markedly positive by puncture test. There was no known clinical sensitivity to castor bean at the time the history and initial skin tests were done. Approximately 2 years later he spread castor bean pomace on his lawn and developed one of his very rare episodes of asthma, moderately severe, and lasting for about 24 hours. He has avoided this antigen carefully for the past 2 years and has had no further asthma.

CASE 13.—C. G., a 27-year-old, white, American housewife, 4 months pregnant. She was first seen in 1951 because of sneezing, coughing, and asthma.

Within a month after moving to the Pasadena area in March of 1951 she began to have attacks of sneezing. About 3 months later she began to cough and wheeze. She came from the Boston area where she had never had anything even resembling hay fever, although she had worked for a number of years in summer camps in the country. A local California physician had treated her cough with diathermy, and had done extensive skin tests. He reported plus reactions to a large number of foods and inhalents, including mink, but none of these reactions appeared to have been diagnostic. A very limited number of skin tests were done in my office and the only positive reaction was a 3 plus by puncture to castor bean. A visit to the home disclosed that *Ricinus communis* was growing in profusion at the back end of her yard. A 5 day course of penicillin, fluids, and iodides cleared up the cough and asthma. Cooperation between her husband and the tract owner has eliminated the castor bean plants. Our winter rains have soaked the ground thoroughly and she is clear of symptoms.

CASE 14.—E. L., a 35-year-old, white, American housewife. She was first seen in 1944 because of asthma.

At the age of 11 the patient chewed up one castor bean and had recurrent abdominal cramps for many months. At the age of 19 she handled a few castor beans and developed marked edema of the eyelids. Some years later she swept out a shack where a bag of castor beans had been stored and suffered her first violent attack of asthma. Puncture reaction to

castor bean, 4 plus; 2 plus to shrimp, crab, lobster (which caused clinical angioneurotic edema). She also had positive intradermal reactions to sagebrush and ragweed, with a history of clinical hay fever from sagebrush.

CASE 15.—R. O., a 7-year-old, white, American schoolgirl. She was first seen in 1950 because of asthma.

This child had many skin reactions, both to puncture and intradermal tests, among them being a 2 plus puncture to castor bean. Although no correlation between this skin test and clinical castor bean allergy is known, the family was warned of the possibility.

CASE 16.—A. S., a 29-year-old, white, American housewife. She was first seen in 1949 because of asthma and eczema.

This patient is included only because of her 4 plus puncture reaction to castor bean dust. She also had large puncture reactions to house dust, cat, Bermuda grass, and olive pollens. Treatment with the inhalants other than castor bean has resulted in alleviation of symptoms. She has been warned about castor bean sensitivity and has so far avoided contact with it. At least we have no knowledge of asthma from contact with the castor bean dust.

CASE 17.—E. E., a 14-year-old, white, American schoolgirl. She was first seen in 1948 because of asthma.

This is not specifically a castor bean case, although she did have a 2 plus puncture reaction to the antigen. She was specifically sensitive to peanuts and other nuts by skin tests and clinical experience. There has been no clinical history of asthma from castor bean dust.

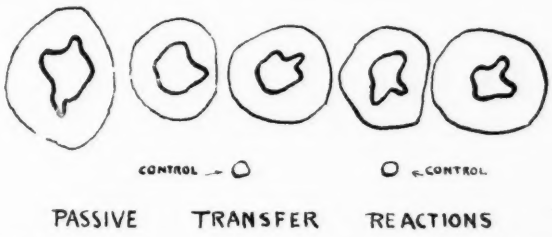

Fig. 1.—Serum which sensitized these sites was taken from 5 castor bean-sensitive patients. Challenged with 1:10 crude extract of castor bean puncture method.

The history of the castor oil industry in Los Angeles dates back to 1933, at which time the California Flaxseed Products Co. began pressing the oil from a few thousands pounds of castor beans. They have continued this part of their business ever since, with an annual production of anywhere from 100 to 900 tons of oil. Since the ricin remains in the cake after pressing, this residue, "pomace," although high in nitrogen (6 per cent), phosphorus (2 per cent), and potash (1 per cent), has no value except as a fertilizer.

In 1946 the Baker Castor Oil Co. built a plant in Los Angeles, and in 1951 produced in the neighborhood of 7500 tons of castor oil. Since the castor bean is approximately 50 per cent oil, it follows that the Los Angeles plant is producing 7500 tons of castor bean pomace. This is at least a tenfold increase in the last 5 years.

Investigation of local dealers in fertilizer disclosed that castor bean pomace sells for less than half the price of cotton seed meal, and has approximately the same qualities. It is, therefore, not surprising that it is being extensively used for lawns, shrubs, and flower beds in the Los Angeles district.

Nationally, the picture is also one of increasing production. During the decade of 1940 to 1950 the annual consumption of castor oil by United States

industry has been approximately 75,000 tons. United States consumption from 1930-1940 was not over 30,000 tons annually.

The chemistry of the castor oil molecule is the reason back of the increasing demand. There is at present no satisfactory substitute for industrial use, and the Baker Company alone has developed over 150 different uses for the oil or fractions of it. Industrially, it is important in paints, varnishes, lacquers, plastics, rayon, nylon, asphalt tile, rubber, textiles, cosmetics, ink, electrical insulations, fungicides, rubber products, soap products, and artificial leather. It is used also very extensively in jet engines, hydraulic and brake fluids, recoil mechanisms, military all purpose grease and explosives.

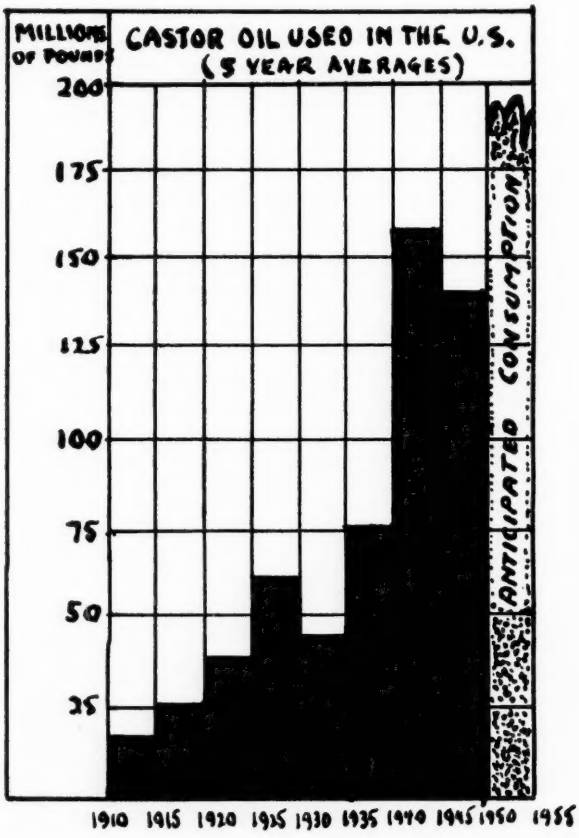

Fig. 2.

Since the demand for oil is so great and since our entire source of the beans was of foreign origin, the United States Federal Government has been promoting the domestic raising of the beans. They have worked closely with the Baker Castor Oil Co. in the development of proper seed, and the United States Department of Agriculture has guaranteed a minimum price of 10 cents per pound to the farmer on home grown beans. Harvesting and hulling machinery has been developed. In 1949 less than 100 acres were cultivated. In 1950 this figure

jumped to 9000 acres, and in 1951 to 84,000 acres. California and Arizona raised 30,000 acres of beans in 1951, and Texas and Oklahoma most of the balance. The national goal for 1952 is 200,000 acres. If this is achieved we may expect a domestic production of 100,000,000 pounds, or approximately one-fourth of our present need.

Those who deal with castor bean products other than castor oil or derivations of the oil should be aware of two potential hazards: (1) the toxic albumin ricin and (2) the castor bean allergen. The toxic component ricin is universally poisonous to man and other mammals. The castor bean allergen possesses no inherent toxicity in the absence of specific sensitivity. Since the Baker Company

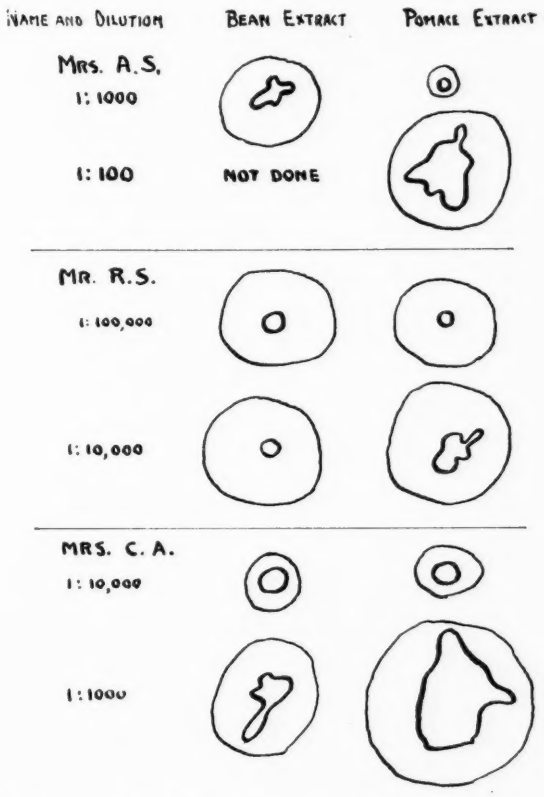

Fig. 3.—Comparison between extracts of castor bean and castor bean pomace (Baker C. O. Co.) Direct skin tests—puncture method.

showed me some evidence that its pomace contained less ricin than pomace manufactured by another which does not use the final solvent-extracting procedure, it occurred to me that the antigenicity of its product might be correspondingly lower. I felt, therefore, that this paper would be incomplete unless the antigenicity of Baker pomace was compared directly with an extract of the bean. Tenfold dilutions of the two antigens were made and tested by puncture on the backs of three of the patients. It will be seen from the charts

that the bean antigen is not more than 10 times as potent as the pomace. In one instance they appear to be about the same. This pomace has been subjected to solvents at high temperature and finally to live steam.

DISCUSSION

The California Flaxseed Company has found an incidence of 2½ per cent clinical sensitivity to castor bean among its small group of employees. In El Centro at the loading platform where flaxseed, grains, and castor beans are stored and loaded into box cars for shipment, two of their group of ten employees have clinical allergic manifestations when the castor beans are being handled. I was unable to find any record of trouble among the farmers who were raising the beans, although sensitivity among farmers who use the pomace for fertilizer is well known in this district.[11]

It is to be remembered that this crop is very new, and another year or two may well be required to show what the incidence of sensitivity is going to be among the persons closely associated with the industry.

The author of an excellent book on allergy[12] devotes only one paragraph to castor beans, and I quote:

"*Miscellaneous Inhalants:* Included in this group are inhalant substances which can provoke allergic symptoms but seldom are encountered in ordinary practice. This is true, for example, of castor bean, which has been responsible for respiratory symptoms in pharmacists or laboratory workers who handle these beans. The dust of these beans also has caused asthma in patients living in the vicinity of castor bean mills, and in farm workers or others who work with fertilizer which contains castor bean flour."

The great increase in the national production of castor oil is, I believe, going to take this allergen out of the "seldom encountered" group because of the corresponding increase in fertilizer production and use. I recently received literature from a relatively new company in Oklahoma City, which is producing antigens for doctors. Its brochure listed over 400 different allergens, but castor bean was not in the list, in spite of its proximity to new centers of castor bean production.

Although castor beans have been processed in New Jersey for a hundred years, those of us who live in California, Arizona, Texas, and Oklahoma should be aware that a new industry has been born. Its by-product fertilizer is likely to find its way to faraway places, and due to the potency of this allergen I would suggest that allergists throughout the nation be "en garde."

CONCLUSIONS

1. During the past 5 years I have seen 9 patients with asthma and 2 with hay fever as a result of inhaling castor bean pomace. During the previous 5 years I saw only one.

2. There has been at least a tenfold increase in the production of castor bean pomace in the Los Angeles district from 1946 to 1951. This will probably be increased another 4 times in the next year.

3. Because of the increase in production and the extreme toxicity of the castor bean allergen it is suggested that proper labeling of fertilizers be mandatory.

4. Since it is unsafe to do intradermal tests with castor bean allergen unless the ricin has been removed, it is suggested that all allergists who have not routinely tested to castor bean do puncture tests on their patients with a concentrated extract of the bean. The puncture method appears to be entirely safe, whereas even a scratch test, if the scratch is long and deep, may cause a constitutional reaction.

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STUDY TO DETERMINE THE ABILITY OF CORTISONE TO SENSITIZE THE SKIN

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WITH the introduction of cortisone for topical therapy[1-5] it seemed reasonable to undertake a study to determine whether the human skin could be sensitized to it by topical application. Experiments in induced sensitization in human beings have been carried out with a variety of substances and by a variety of techniques.[6-14] In studying any new drug which is to be used topically, for its potential capacity to sensitize the human skin, one or several techniques based on the experimental experiences cited above should be followed.

In the present study two general procedures for inducing sensitization were used. The first employed a technique similar to that used by the writer in experimental sensitization in man,[13, 15] consisting of the repeated application of the excitant by patch test to the skin at spaced intervals. In the present experiment, a larger quantity of the test substance was used, and the duration of contact was prolonged. In the second procedure a plan suggested by Draize[16] of the Department of Pharmacology, United States Food and Drug Administration, was followed. In summary, repeated short patch test exposures with the excitant are made at short intervals to various parts of the body, and finally a challenging test is made two weeks after the last test.

FIRST PROCEDURE

The patch consisted of a ¾ inch (1.8 cm.) square pad made of multiple layers of gauze, attached to a 1½ inch (3.8 cm.) square of waterproof adhesive tape. The gauze pad was saturated with 0.1 ml. of cortisone (Cortone, Merck) containing 2.5 mg. of the drug. The patch was applied to the lateral surface of the subject's arm, and was reinforced by a wide strip of adhesive tape, in order to help retain the moisture in the pad as long as possible. Two variations in technique were followed. In one group the first test was removed after a period of three days. If no reaction appeared, a second patch was applied fourteen days after the first, to an adjacent area of the skin, for another 3 day period. In the absence of reaction, a third and final patch was placed on an adjacent skin site seven days after the second treatment. The patch was removed after seven days and the site kept under observation for several weeks thereafter. In the other group of subjects the skin was first treated for seven days and, in the absence of any reaction, an adjacent skin area received a second patch two weeks after application of the first. This was kept in place for 7 days, and the skin sites observed for several weeks thereafter.

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Received for publication, Jan. 28, 1952.

SECOND PROCEDURE

The patch test was prepared as in the first procedure. It was applied to the left forearm and removed in 24 hours. A second patch test was then placed on the right forearm one day after removal of the first, and was retained for 24 hours. In similar manner additional patch tests were applied every other day to widely separate areas of the body, in the following order: medial aspect of left arm, medial aspect of right arm, left subclavicular area, right subclavicular area, left upper back, right upper back, lower left thigh, and lower right thigh. A total of ten tests was employed. No test was applied on a Sunday, so that the interval between the third and fourth and sixth and seventh tests was 48 instead of 24 hours. A challenging 24 hour test was applied to the upper left forearm two weeks after the tenth or final application.

Twenty subjects were treated according to the first procedure. They were patients in the allergy clinic, under observation for nasal and bronchial allergy. There were 19 women and 1 man, ranging from 18 to 63 years of age. Ten subjects were treated according to the first plan of study (an initial 3 day patch test) and eight according to the second (an initial 7 day application).

In 18 of the subjects observation was continued for 28 to 35 days after the final patch test. In two subjects, not completely treated, the final application had not been made. They were observed for only 7 days after the last patch test.

Twenty-four subjects were treated in accordance with the second procedure. There were 23 unselected student nurses, from 17 to 23 years of age, and one instructor, 30 years of age. The sites were observed during the entire course of the study, and for at least a week after the final challenging dose.

RESULTS

Active sensitization could not be demonstrated in any of the subjects. It is of interest to note that one patient treated by the first procedure presented pigmentation at the site of the initial 3 day patch test. This lasted for five weeks. The two subsequently treated sites did not show any change in color. In another subject in the same group the last site treated (7 days) showed slight darkening at the first inspection, but there was no change in skin color when the subject was seen one week later.

DISCUSSION

Schwartz[17] has recommended a 48 hour contact test and its repetition in 14 to 21 days, as a provocative means for determining the sensitizing capacity of a substance. In the present study three variations in technique were employed to determine the potential sensitizing hazard of locally applied cortisone. A 7 day exposure was employed in one group of the subjects, because it had been determined by the writer in previous experimental studies[13, 15] and unpublished observations that a single exposure with krameria for seven days was successful in sensitizing 70 per cent of the subjects, whereas the maximum incidence of sensitivity induced by repeated shorter applications of the

excitant was not over 90 per cent. The use of one or two prolonged exposures has the advantage of shortening the period of observation and of requiring fewer visits by the subject being tested.

In sensitizing human beings with dinitrochlorobenzene, Wedroff and Dolgoff[11] had employed a single drop of a 10 per cent solution of dinitrochlorobenzene by the drop method. Since in the present study the period of contact was a more prolonged one than is usually employed, there had been utilized a more intense stimulus than was generally needed for active antigens. There is no implication in these statements that concentrations of different sensitizing substances are being compared, for that concentration which can provoke sensitization must be established for each antigen individually. It is a well-known fact, moreover, that contactants vary in their capacities to sensitize[21] and, for this reason, it is advantageous to have available several methods for the study of potential sensitizing substances.

The procedure for testing suggested by Draize[16] has merit in that a larger and more varied part of the body surface is exposed to short, repeated stimuli with an excitant. This plan of study would involve a potential hazard to the test subject, however, were an active excitant employed. Then the occurrence of sensitivity could be followed by the spontaneous flare of one or more of the sites of treatment.[18, 19, 20]

Though study of a larger group of subjects would be desirable, the findings in 44 human beings are presented for the reasons discussed above. The presence of negative findings would seem to indicate the absence of an antigenicity or, at least, a low antigenicity of the substance under study. Whether cortisone possesses any antigenicity in clinical eczematous contact dermatitis would have to be determined by study of a larger series of subjects and the use of longer periods of application.

Two of the subjects showed darkening of the skin at one of the sites of application. The significance of such a finding cannot be stated. Hyperpigmentation has been reported[22] in patients receiving cortisone therapy.

SUMMARY

A study to determine whether the human skin could be sensitized by patch test applications of cortisone yielded negative results in 44 subjects. Two procedures were employed: (1) initial prolonged patch test exposures for 3 to 7 days followed by a 7 day challenging dose, and (2) frequent, short (1 day) exposures followed by a short challenging exposure. Within the limits of the described experiments, it would appear that cortisone is not an active cutaneous sensitizer.

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IS SKIN TESTING IN ALLERGIC PATIENTS WORTH THE EFFORT?

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TO DETERMINE the value of skin testing to foods and inhalants 1,900 allergic private patients were studied. Tables I and II represent a breakdown of the 1,900 patients. There were 1,104 females and 796 males. A total of 131,865 skin tests were carried out on this group with no deaths. This was an average of 70 tests per patient. The infants received relatively fewer tests in comparison with the older age groups because of the limited variety of foods eaten at this age. Tables III and IV show the reactions to the various allergens. In this series, a negative reaction meant that no difference was noted from the general average of clearly nonreactive tests. A local reaction with edema covering approximately twice the area as the negative was a 2 plus. Local edema (not enough to cover twice the area but more than the negative) was a 1 plus. A reaction larger than 2 plus but without pseudopods was a 3 plus. When pseudopods are present the reaction is designated as a 4 plus. One plus or doubtful reactions may represent a clinical offender at times and yet the large number of doubtful reactions obtained make it impractical to attach too much significance to them. Chocolate, cow's milk, wheat, tomato, malt, corn, orange, black pepper, and coffee, in that order of frequency, were found to lead the list of food reactions. Inhalant reactions in West Texas are led by Russian thistle and followed in order by Bermuda grass, house dust, tobacco, chicken feathers, ragweed, and cow hair. All of the extracts used for testing in this study were purchased from approved laboratories.* Some of the extracts had to be diluted because reactions were consistently obtained on normal individuals.

SAFETY

Probably the most important factor in evaluating any procedure in medicine is whether or not it is dangerous. The old saying, "If no good can be done, at least do no harm," is applicable to any test. In this fairly large number of skin tests, there were no deaths and no serious reactions. An aggravation of the symptoms of the allergic state for which the patient was being tested was the only untoward reaction encountered. Deaths have been known to occur from skin tests, but from this series it would seem that the procedure is safe if a few precautions are observed. First of all, it should be kept in mind that little is to be gained by testing a patient to a food or inhalant that is known to give clinical symptoms. Since the known offending agent should be eliminated regardless of the result of the skin test, the possibility of a severe reaction or even death must not be forgotten. In this series, many of the patients were not tested to agents that were known to give severe reactions in daily life. The questionable agents were first tested by the scratch method and if the

Received for publication, Jan. 9, 1952.

*Abbott Laboratories, Lederle Laboratories, and Arlington Chemical Co.

TABLE I. TYPES OF ALLERGIC DISEASE IN 1900 PATIENTS

TYPES	NO.
Hay Fever	875
Atopic Eczema	418
Asthma	279
Urticaria	147
Other Allergies (Gastrointestinal allergy, migraine, etc.)	181
Total	1900

results were negative, were followed by intradermal testing. Routinely, all patients below the age of 12 and over 60 years were tested by the scratch method first. Reactions occurring from scratch tests, of course, are more easily controlled than those resulting from intradermal injection since wiping off of the allergen will usually control the reaction.

POSITIVE REACTIONS

Numerous writers[1] over the past twenty years have stressed the fact that a positive skin reaction does not invariably mean clinical sensitivity to that allergen. Sixteen per cent of the skin tests performed in this series gave 2 plus or stronger skin reactions. Of these positive tests, it is difficult to give an accurate estimate of the actual clinical sensitivity that this group embraces. The patient's observations may be very misleading in some instances, while in others their underenthusiasm for following allergic instructions make the clinical evaluation of skin tests impossible. These facts are of major importance when skin tests are being evaluated. Most allergists agree that skin testing to inhalants and pollens is a valuable procedure. However, when the subject of testing to foods is brought up there is considerable controversy over how many foods should be included routinely and just how much significance can be placed on any positive food test. Of the 1,900 patients in this series, 632 were followed for a sufficient period of time and cooperated enough to unable us to evaluate the positive food tests that were obtained. The twenty foods that reacted most often by skin test are listed in Table V. The other positive food tests were so rarely correlated with clinical sensitivity that they can be ignored. From Table V it will be noted that 38 per cent of the positive chocolate skin tests were correlated clinically as causing the hives. Therefore 62 per cent of the positive chocolate skin tests in case of hives may be considered false positives. Also, it will be noted from the table that while coffee, spinach, pear, cantaloupe, cinnamon, beans, and grapes gave a high incidence of positive tests, there was no actual clinical importance of these foods. Egg white ranked six-

TABLE II. AGES OF ALLERGIC PATIENTS

AGE GROUPS	NO.
Infants	211
2-12 yrs.	398
12-60 yrs.	1256
Over 60 yrs.	35
Total	1900

TABLE III. POSITIVE INHALANT REACTIONS

	2 PLUS	3 PLUS	4 PLUS	TOTAL NO.
Russian thistle	239	86	45	370
Bermuda grass	268	55	28	351
House dust	225	53	11	289
Tobacco	203	67	14	284
Feathers (chicken)	240	37	5	282
Ragweed	189	52	17	258
Cow hair	211	39	1	251
Wool	203	35	2	240
Johnson grass	173	38	21	232
Pyrethrum	193	25	0	218
Kapok	193	23	0	216
Cat hair	165	9	2	176
Dog hair	157	8	0	165
Mountain cedar	126	27	6	159
Rayon	144	12	1	157
Tragacanth	132	0	6	138
Horse hair	109	10	3	122
Careless weed	102	16	4	122
Silk	94	12	0	106
Orchard grass	81	15	2	98

Less Frequent Positive Inhalant Reactions (Total No.).—Goat hair 97, rabbit hair 89, cocklebur 78, pigweed 67, guinea pig hair 63, elm 57, sagebrush 49, horse dander 48, sycamore 47, camel hair 38, flaxseed 27, alternaria 21, hormodendrum 20, jute 20, sweet vernal grass 17, June grass 17, karaya 9, timothy 9, hickory 8, marsh elder 8, burning bush 6, walnut 5, pine 5, and maple 3.

TABLE IV. POSITIVE FOOD REACTIONS

	2 PLUS	3 PLUS	4 PLUS	TOTAL NO.
Chocolate	381	77	9	467
Cow's milk	380	52	4	436
Wheat	324	75	14	413
Tomato	261	67	9	337
Malt	272	35	6	313
Corn	263	29	8	300
Orange	247	35	3	285
Black pepper	213	38	5	256
Coffee	218	29	3	250
Cottonseed	199	39	5	243
Oats	208	17	4	229
Spinach	204	20	1	225
Pear	156	55	4	215
Cantalope	170	41	4	215
Banana	188	22	1	211
Egg white	187	18	4	209
Cinnamon	179	30	0	209
Navy bean	191	13	4	208
Grape	175	30	3	208
Halibut	186	16	3	205

Less Frequent Positive Food Reactions (Total No.).—Lemon 202, mustard 202, apple 193, nuts 187, carrot 186, hops 186, grapefruit 181, soybean 177, dates 176, peas 172, pork 170, white potato 170, apricot 163, asparagus 163, rye 161, strawberry 160, peach 160, raisin 155, rice 155, pumpkin 154, whole wheat 154, parsley 151, cauliflower 151, nutmeg 149, pineapple 145, cherry 145, string bean 141, lettuce 141, tea 140, mushroom 138, beef 135, clove 134, raspberry 133, squash 131, blackberry 131, peanut 131, cabbage 131, green pepper 130, blackeye pea 128, chicken 127, fish 124, sweet potato 122, plum 121, lamb 118, broccoli 116, watermelon 116, cranberry 115, prune 115, beet 115, celery 114, cucumber 110, turnip 106, onion 103, watercress 102, barley 101, radish 99, buckwheat 96, coconut 94, vanilla 92, pecan 90, almond 89, rhubarb 87, veal 85, turkey 84, bass 83, shrimp 82, liver 73, olive 73, goat milk 67, salmon 63, sardine 63, allspice 60, eggplant 57, oyster 54, sage 50, black walnut 50, fig 50, tangerine 49, English walnut 36, bay leaves 29, ginger 28, caraway seed 27, egg yolk 25, anise 25, tuna fish 18, currant 18, lime 16, parsnip 8, and haddock 3.

teenth in the list of positive skin reactions but was one of the most important in the clinical evaluation. From this study, it is questionable whether one is justified in routinely testing patients to many foods. A positive food test that has less than 25 per cent chance of being important clinically would seem to be wasted effort. Therefore, on the basis of Table V, patients with urticaria should be tested routinely to only six foods—chocolate, milk, wheat, orange, cottonseed, and egg white. Hay fever and asthma patients should be routinely tested to chocolate, milk, corn, wheat, a spice (black pepper), egg white, and fish (halibut). Atopic eczema in children would seem to require routine testing to milk, wheat, egg white, tomato, malt, corn, orange, banana, and fish (halibut). Adult atopic eczema should require very little food testing routinely—to egg white only. Any food that a patient suspects should also be added to the routine group of tests.

TABLE V. PER CENT OF POSITIVE SKIN TESTS OF CLINICAL IMPORTANCE
(BASED ON 632 PATIENTS ACCEPTABLE FOR REVIEW)

	HIVES	HAY FEVER	ASTHMA*	ECZEMA (CHILD)	ECZEMA (ADULT)	MISCELLANEOUS
Chocolate	38	47	29	16	5	0
Cow's milk	25	31	58	92	22	25
Wheat	66	35	33	61	9	33
Tomato	6	5	16	50	7	25
Malt	0	6	4	33	16	0
Corn	12	16	29	33	0	33
Orange	40	18	10	44	0	0
Black pepper	0	33	33	0	0	0
Coffee	0	0	0	0	1	0
Cottonseed	25	18	19	0	0	0
Oats	0	18	8	0	0	0
Spinach	0	0	0	0	0	0
Pear	0	0	0	0	0	0
Cantalope	0	0	0	0	0	0
Banana	0	15	10	50	0	0
Egg white	74	36	73	62	66	0
Cinnamon	0	11	8	0	0	0
Navy bean	0	0	0	0	0	0
Grape	0	0	7	0	0	0
Halibut	14	25	25	50	0	0

*Many of the asthmatic patients also had hay fever but are included only under the chief complaint.

NEGATIVE REACTIONS

It is also accepted that individuals known to be clinically sensitive to foods and inhalants may show negative skin reactions to these allergens.[2] It cannot be accurately estimated how many of the negative tests in this series were clinically false negative tests. Many of the patients proved to be unable to eat foods or tolerate inhalants that gave negative reactions. Many others due to poor cooperation, could not be followed closely enough, to determine the presence of false negative tests. Since no difference was noted in the various commercial extracts used, it is believed that false positive and negative tests in known sensitive patients will occur regardless of which presently available commercial extracts are used or how much care is exercised in testing. It is possible that different types of skin testing material, such as raw foods[3] and other methods of

testing, such as the iontophoretic method[4] will, in the future, reduce the number of false negative and positive reactions. Although these facts will detract from the value of testing, they should not cause the procedure to be ridiculed or eliminated from the allergy study of a patient. Many helpful clues may be discovered by routine skin testing and the mystery of the cause of the allergic state may be cleared up very easily.

VALUE OF SKIN TESTING

From these confusing facts, one can justly question the value of skin testing. However, the interpretation of the tests, as in most other tests in medicine, will determine their value when applied to the clinical handling of the particular case. To discover the cause or causes of a patient's allergy will often require the physician to use every diagnostic tool at his command. The best diagnostic tool in allergy is a careful history of events, conditions, and other factors relating to the present illness. It is certainly the fastest and least expensive of the methods available to find the clues that will lead to the cure of an allergy. Not infrequently, this is all that is needed for the successful handling of the case. For example, if the patient states that his asthma occurs only after he sprays disinfectant about the room, nothing further need be done in order to advise the patient intelligently. If the history reveals milk as an offender and yet the patient is eating milk products, a trial period without milk and milk products for one week may be all that is necessary to bring about a cure. Any suspicious food brought out by the history should be eliminated for one week to see the effect. Any suspicious inhalant (perfumes, disinfectants, etc.) should be eliminated in the same way. If careful history taking reveals few or no clues of importance, then skin testing will probably serve as a short cut to the finding of the offending agent. Patients must be impressed with the fact that positive tests are only clues and that the corresponding allergens must be eliminated to determine their importance in the particular illness at hand. To skin test a patient and give him a long list of positive offenders and not instruct him as to their significance is poor practice of medicine. Patients must also be told the foods that contain the offender to be eliminated. For example, to tell the patient to eliminate milk and not remind him that butter is a milk product may make the difference between success and failure in relieving his allergy.

EMPIRICAL PROCEDURES

Too often, careful history and elimination of suspects brought out by skin testing fails to reveal the allergy secret. The next step must be empirical elimination of foods and inhalants. Various trial diets may be used, such as those advocated by Rowe.[5] The elimination of most of the inhalants can also be tried on an empirical basis. This is best accomplished during months of the year when wind-borne pollen and molds are at a minimum. To isolate a patient in a clean room stripped of everything except a canvas cot for several days will bring out the importance of such common offenders as wool, feathers, orris root products (perfumes, powders, etc.), dog hair, and others. If several days of such isolation causes marked improvement, as is the case occasionally,

the various materials can be introduced into the room one by one to notice the clinical effect. These empirical methods of food and inhalant elimination are practical commonsense allergy tests.

PSYCHOGENIC FACTORS

In studying a series of allergy patients, one is impressed by the psychogenic factors that not only influence the course of the disease but very often cause the allergic flare-up. Sir William Osler as far back as 1912 noted the neurotic elements in asthma.[6] These factors are particularly evident in such allergies as hives, atopic eczema, gastrointestinal allergy, allergic migraine, and occasionally in asthma. Too often, for example, patients gave strong positive reactions to such foods as chocolate and on study it seemed that chocolate was the cause of asthma. However, after a marital disagreement had subsided, chocolate could be eaten with no further difficulty. This naturally cast considerable doubt upon the value of that positive chocolate reaction. It is possible, however, that the psychogenic factor acts as the trigger mechanism enabling the chocolate to cause the asthma. When the psychogenic factors are removed, chocolate can again be eaten without symptoms until another factor sets off the trigger mechanism.

SUMMARY

1. The results of 131,865 skin tests, performed on 1,900 allergic patients, are studied.

2. Chocolate, cow's milk, wheat, tomato, malt, corn, orange, black pepper, and coffee, in that order of frequency, led the list of food reactions.

3. Russian thistle, Bermuda grass, house dust, tobacco, chicken feathers, ragweed and cow hair led the inhalant reactions in West Texas.

4. Food testing is time consuming, expensive, and unimportant in most instances. The foods that should be tested in hives, hay fever, asthma, childhood, and adult eczema are indicated.

5. Skin testing is a safe procedure if proper precautions are observed.

6. Skin testing is worth the effort since it very often serves as a short cut to the finding of the offending agent.

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IS MIGRAINE AN ALLERGIC DISEASE?

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MIGRAINE has been the happy hunting ground of the theorist, and the problem has been attacked by representatives of all branches of medicine. Each in turn has discovered in migraine phenomena pertaining to his own specialty'' wrote Critchley and Ferguson[3] in 1933. Not the least the allergists have participated in these attacks, and from many textbooks on allergy, one derives the impression that they captured the prey.

Many years before the concept of allergy was formed, some authors thought that migraine had some connection with the diseases which today we call allergic. In his brilliant article on asthma, now almost one hundred years old, Trousseau[9] remarked that he frequently found migraine in persons suffering from asthma. It remained however for the French Lesné and Richet,[7] and especially for the American Vaughan[11] in 1927, to set forth the ideas, that migraine was, or could be, an allergic disease. During the following 25 years much work has been done, but the problem is still unsettled. In several centers migraine still holds its place in the allergy clinic, in others the disease is treated in other departments.

Various circumstances have contributed to the concept of migraine as an allergic manifestation:

1) The most important is that patients with asthma, hay fever or other allergic diseases often have migraine as well, and migraine is found in their families.

2) Several authors have reported a very high percentage of positive skin reactions in migraine patients. Thus, Balyeat and Rinkel[1] were able to find positive skin reactions in every one of their 202 patients and the figures of other investigators are often likewise impressive.

3) By using elimination diets and provocation experiments, Rowe,[12] as well as Balyeat and Rinkel[1] and Randolph[13] claim that they are able to find the offending allergens, and through the exclusion of these, to cure their patients.

4) Clinically, migraine has some resemblance to allergic disorders in its sudden and unexplained appearance and in its typical recurrent attacks.

5) Gansslen[5] found eosinophilia in several of his migraine patients, and considered this as evidence of the allergic origin.

During recent years considerable doubt has been thrown upon the concept of migraine as an allergic disease. Feinberg[4] for instance, does not believe that too many cases of migraine are allergic. Vallery-Radot[10] is of the same opinion. In two recent works from Sweden, neither Hacksell et al.[6] nor Bergquist[2] could find any evidence that migraine was an expression of allergy.

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OWN INVESTIGATIONS

In connection with a current study of the heredity of asthma,[8] the incidence of migraine in the relatives of 191 asthmatics, 200 normal, nonallergic persons, and 50 patients with baker's asthma, was investigated. A total of 3815 relatives for 4 generations were seen. The diagnosis of migraine was based on the following criteria: Attacks of headache, especially if unilateral (hemicrania) accompanied by nausea, and often vomiting, and followed by prostration. Visual disturbances (scotomata or blind spots) occurred in about a quarter of the cases, and when found were typical. Auditory disturbances were much less common. Paraesthesias, especially of the fingers, were seen occasionally.

Incidentally, this investigation showed that secondhand information about heredity may be extremely misleading. The data here were obtained in each case by personal contact with the relatives. The relatives of the asthmatics and of the normal persons were found to be of the same ages and of quite comparable physical characteristics and social character. The relatives of the patients with baker's asthma were of somewhat older age groups and they cannot be compared directly with the two other groups. Table I shows the figures.

TABLE I. FREQUENCY OF MIGRAINE IN THE GROUPS OF RELATIVES OF ASTHMATICS, NORMAL PERSONS AND PATIENTS WITH BAKER'S ASTHMA

		NUMBER OF RELATIVES EXAMINED		NUMBER OF RELATIVES WITH MIGRAINE		NUMBER OF RELATIVES WITH MIGRAINE IN PER CENT	
	NUMBER	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
Asthmatics	191	777	857	20	65	2.57	7.59
Normal persons	200	855	935	13	61	1.52	6.54
Baker's asthma	50	188	203	3	9	1.60	4.43

Table I shows that migraine is common—especially among women—but one will note, that there is only a very slight difference between the incidence of migraine in the three groups of relatives. The result shows that there is no hereditary relationship between migraine and asthma. Further it shows that migraine is so frequent, that one may expect to find this disease in practically any family, if one contacts a reasonable number of relatives. Quite another question is the heredity of migraine by itself; although it cannot be discussed here, it should be mentioned that the evidence is in favor of simple dominant heredity.

A total of 171 patients with migraine was found among the 3815 persons interviewed. All of these were questioned about the cause of their migraine attacks. Most ascribed their headaches to "nervousness," worries or strenuous mental work, but not one of the 171 patients in this series gave a history of exogenous factors of probable allergic nature. Special attention was paid to the possible relation between the headaches and food but in spite of careful questioning no definite relation could be found in any patient. It must be admitted that this questioning does not by itself exclude the possibility of allergy to food as being involved in the mechanism of migraine, but it is surprising that not even a suggestion of such a mechanism was found. Studies of

food by the elimination of one item or the other were not made, as most of the patients were seen only once or twice. Skin tests and counts of the circulating eosinophils with the Dunger technique were made in a number of patients, selected because they had migraine by itself and without other allergic diseases. The results are shown in Table II. Although the total number of patients

TABLE II. SKIN TESTS AND CIRCULATING EOSINOPHILS IN MIGRAINE PATIENTS AND IN NORMAL, NONALLERGIC PERSONS

	SKIN TESTS (INTRACUTANEOUS)			
	TOTAL NUMBER INVESTIGATED	ALL SKIN TESTS NEGATIVE	ONE OR MORE SKIN TESTS POSITIVE	PER CENT WITH POSITIVE SKIN TESTS
Normal, nonallergic persons	208	168	40	19.2
Migraine patients	40	30	10	25.0

	CIRCULATING EOSINOPHILS			
		0-399 CIRCULATING EOSINOPHILS CU./ML.	≧400 CIRCULATING EOSINOPHILS CU./ML.	PER CENT WITH EOSINOPHILIA (≧400 EOSINOPHILS/ML.)
Normal, nonallergic persons	710	661	49	6.9
Migraine patients	55	52	3	5.8

examined is not great, it is clear that migraine patients and normal nonallergic persons do not differ regarding the frequency of positive skin reactions or eosinophilia. The small differences are not statistically significant.

SUMMARY AND CONCLUSIONS

1) The incidence of migraine among the 3815 relatives of 241 asthmatic patients and of 200 normal, nonallergic persons, was found to be identical.

2) This shows that migraine has no hereditary relationship with asthma.

3) Of 171 migraine patients, none gave a history of probable allergic factors eliciting their headaches. Skin tests and circulating eosinophils did not differ from values obtained on normal, nonallergic persons.

4) It is concluded that migraine is probably only rarely of allergic nature.

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MIGRAINE IS AN ALLERGIC DISEASE

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MIGRAINE has been a problem disease throughout the 5,000 years during which it has been recognized. Many theories have been advanced to explain the peculiar and characteristic events which constitute the syndrome known as migraine. The picture has been further confused recently by emphasis on syndromes having only some of the characteristics of true migraine; these are known as "migraine variants" and "migraine equivalents." In this review, we shall consider only true migraine, defined as follows:

> Migraine is a syndrome, usually hereditary, characterized by periodic unilateral headaches, with complete freedom between attacks. Attacks are often preceded by an aura (most frequently visual) and associated with nausea, with or without vomiting. In our opinion, migraine is an allergic disease.

Migraine has been recognized since 3,000 B.C. Among early contributors were Aretaeus, Galen, Caelius Aurelianus, Tissot, and Brinton. Liveing published an entire book upon the subject in 1873.[23] In the same year, Latham[22] first suggested the modern theory of mechanism. LaRoche, Richet, and St. Girons[21] and Brown[4] suggested allergy as a cause of migraine. Vaughan[29] obtained good results with elimination diets. Many others have since repeated his work. Wolff[33] and his co-workers have performed most of the monumental experimental work upon which the present-day theory of mechanism is based. Goltman[11] proved that cerebral edema occurred during attacks of migraine (induced by wheat).

The accepted theory of mechanism of migraine was worked out primarily by Wolff.[33] Prodromal symptoms are due to cerebral vasoconstriction. This is demonstrated by clinical experiments in which vasodilating agents such as amyl nitrite caused temporary abolition of scotomata (with no change in blood pressure).

The headache pain is due to dilatation of branches of the external carotid artery. This is based upon a series of experiments: Pool and Nason[25] showed that ergotamine tartrate in animals caused vasoconstriction of arteries of the dura, rather than the pia or the brain surface. Graham and Wolff[13] then proved that diminution in pulsations of the temporal and occipital arteries closely paralleled relief of migraine pain (by ergotamine tartrate). During migraine, the superficial arteries of the affected side are more prominent than contralateral vessels. Also, ligation of these arteries leads to temporary obliteration of certain pain areas.

Pressure on the common carotid on the affected side relieves the headache; contralateral pressure may increase it. Intensity of pain is not related to changes in cerebral veins. Any measure which reduces cranial arterial pressure will

TABLE I. FAMILY HISTORY OF MIGRAINE AND OF OTHER ALLERGIC DISEASES

	NUMBER OF PATIENTS	MIGRAINE		OTHER ALLERGIES	
		POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Migraine only	23	13	10	12	11
Migraine and other allergies	32	13	19	24	8
All patients	55	26	29	36*	19

*Other allergies—Incidence:

Bronchial asthma	22
Hay fever	17
Perennial allergic rhinitis	7
Urticaria	4
Atopic dermatitis	3
Nasal polyps	3

lower pain intensity. Goltman has shown that cerebral edema is present during migraine; it appears and subsides synchronously with the pain. This edema links migraine to other allergic diseases, in which edema is a main feature.

Continued dilatation of cerebral arteries leads to actual edema and thickening of the arterial walls; this explains the ineffectiveness of ergotamine in late stages of an attack. Associated with the headache proper is painful contraction of head and neck muscles; this ache may persist after the migraine itself has subsided.

Positive family history of migraine has been reported in over 60 per cent if migrainous patients; high family incidence of other allergic diseases has also been reported. Our figures are shown in Tables I and II. Our statistics are biased by the fact that many patients came to us for treatment of other allergic diseases; therefore, family incidence of other allergic diseases is unexpectedly high.

Allergy to foods has, in our experience, been the prime precipitating cause of true migraine. Patients who have frequent attacks (more often than every six weeks) are usually sensitive to foods eaten in some form almost daily. It has been known for centuries (and never properly explained) that, after a migraine, there is a latent period during which no ill effects follow stimuli which ordinarily cause attacks. Because of this, such everyday foods as milk or wheat may cause headaches as infrequently as once or twice a month. The following case is an example of this:

CASE 1.—Miss E. H., a 33-year-old, white, medical secretary, had sick headaches for 18 years. They now occur every 1 to 2 weeks. She develops increased appetite shortly before onset of pain. Pain is mostly over right eye, severe and throbbing. Nausea and vomiting

TABLE II. OTHER ALLERGIES IN 55 PATIENTS WITH MIGRAINE

None	22
Present	33
Hives	18
Hay fever	13
Perennial allergic rhinitis	12
Bronchial asthma	8
Gastrointestinal allergy	5
Nasal polyps	3
Atopic dermatitis	1

follow two hours later, although she does not vomit with every attack. Spells last 24 to 48 hours. No association with menses. They occur often on week ends and frequently follow aggravation. Past history noncontributory. Complete previous examinations of eyes, ears, nose, and throat were normal. Blood pressure remains normal during attacks. Sugar did not relieve the headaches. Complete physical examination, urine, blood count, and Kahn test revealed no abnormalities. Previous ineffective medications include sedatives, bromides, antihistaminics, vitamins, nicotinic acid, methyl testosterone, ergotrate maleate, Gynergen, Bellergal, nitroglycerine, caffeine, and thiamine. Cafergot gave slight relief.

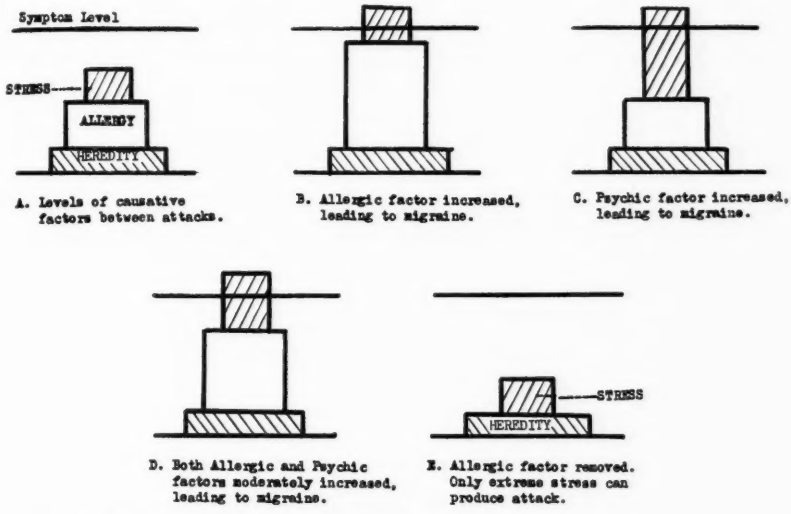
Symptom Level
STRESS
ALLERGY
HEREDITY
A. Levels of causative factors between attacks.
B. Allergic factor increased, leading to migraine.
C. Psychic factor increased, leading to migraine.
D. Both Allergic and Psychic factors moderately increased, leading to migraine.
STRESS
HEREDITY
E. Allergic factor removed. Only extreme stress can produce attack.

Figure 1. Relation of Allergy and Stress to Migraine attacks.

The patient rarely drank milk, because it usually gave her diarrhea. Because of this, she was placed on a milk-free diet; one week later, she was given a milk feeding test, consisting of two feedings of milk, one hour apart. A leukopenic index done at this time had equivocal results, with white cell counts (at 20 minute intervals) of 7,150, 8,750, 7,850, 6,700. Two hours after the second feeding of milk, she developed the worst migraine she has ever had, with severe pain, primarily on the left side, and vomiting which persisted for twelve hours steadily. The headache lasted over a period of 36 hours.

She was maintained on a milk-free diet during succeeding months. Her attacks of migraine have disappeared completely, although she has had mild generalized tension headaches on occasion. Pork gives her a slight headache and nausea if she eats it in large quantities. Despite the fact that she has remained at the same job and under the same stresses, she has had no migraine attacks for almost two years.

Chocolate is the most common cause of migraine, but most patients sensitive to it only find out for themselves and never consult a doctor. Patients who have attacks at long intervals usually know they are due to an obvious or exotic food. Other authors have reported cases of true migraine due to inhalant allergens; we have seen none of these. Table III lists the proved causes of migraine in our patients.

Some attacks of migraine follow unusual mental strain or psychic trauma; they occur either during the stress period or upon relaxing afterward. Attacks of any other allergic disease (i.e., hives, asthma, atopic dermatitis) may also

TABLE III. FOODS KNOWN TO CAUSE MIGRAINE (45 PATIENTS)

Milk* †	15	Fruits	7
Chocolate†	14	Apricots	
Wheat†	10	Raspberries	
Pork†	8	Watermelon	
Other meats	2	Prunes	1 each
Egg†	2	Apple	
Fish	2	Citrus fruits	
Shellfish	2	Pears	
Coffee	2	Miscellaneous	9
Vegetables	14	Chicken	
Peanuts	3	Corn	
Onions	2	Root beer	
Celery	2	Molasses	
Potato		Pistachio	1 each
Tomato		Caraway seed	
Soybeans		Sugar (beet, cane, corn) †	
Peppers	1 each	Garlic	
Asparagus		Yeast	
Endive		Liquor (?)	2
Broccoli family		Medicines (?)	2

*Patients sensitive to milk are also sensitive to the common forms of chocolate because they contain milk.

†Only these foods were sole causes of migraine; all others were instances of multiple causes in individual patients.

follow periods of stress. The mechanism of this relationship between psyche and allergy is shown schematically in Fig. 1. Here we note that either psychic or allergic stimuli or a combination of both can precipitate clinical symptoms. When allergy is completely controlled, it is very difficult, although not impossible, for psychic stimuli alone to provoke symptoms. This can also be reversed to explain the good results sometimes achieved by psychotherapy. The analogy can be extended to other allergic diseases, although the psychic factor is variable in importance. Other factors can also be added, particularly the endocrine, to explain the premenstrual migraines.

Thus, we do not deny that psychic factors are important in migraine. They are not, however, the prime factor, although they may be the most obvious. Control of allergic factors will, in most patients, completely control symptoms (vide infra). Migraine should not be labeled a "psychogenic" disease, nor should the patient be considered "psychopathic."

Other contributory factors include visual defects (of minor importance) and endocrine factors. Most women have attacks with menstruation; they usually

TABLE IV. AURA WITH MIGRAINE HEADACHES
(55 Patients)

Aura present:	34
Visual	21
Fatigue	9
Excess energy	3
Heaviness head & neck	5
Irritability	2
Sneezing	2
Urinary frequency	1
Nausea	1
Yawning	1
Aura absent:	21

TABLE V. SEX AND AGE AT ONSET OF MIGRAINE
(55 Patients)

AGE	MALE	FEMALE	TOTAL
5 - 9	3	10	13
10-14	2	7	9
15-19		8	8
20-24	4	12	16
25-29	1	5	6
30-34	1	2	3
Total	11	44	55

lessen during pregnancy and after menopause. The reason for this is not known, although water retention associated with premenstrual tension may be a factor. True migraine occurs at other times and in both sexes.

SYMPTOMS

The headache is classically unilateral, throbbing, and severe. In later stages, it may become generalized. Periodicity is the most constant feature of the disease. There are no symptoms between attacks, unless the patient also has tension or other types of headaches.

An aura precedes the headache in about 50 per cent of patients (see Table IV). It is variable in type and severity. The classical prodromata are visual, including blurring of vision, scintillating scotomata, etc. Photophobia or other visual symptoms often accompany the headache. Other aura include malaise or excess energy, tinnitus, polyuria, anorexia, etc.

Nausea is a very common feature of classical migraine, leading to the old name "sick headache." The nausea usually appears at the height of the pain; if vomiting follows, the headache is frequently relieved thereafter. However, these features are not diagnostic of migraine, since nausea may follow any severe and prolonged headache.

Sensory disturbances sometimes occur, either as an aura or as part of the headache. Paresthesias are the most common. Motor disturbances such as temporary paralyses are infrequent; of these, ophthalmoplegic migraine is the best known.

Laboratory findings have shown no consistent abnormalities. Tests done included urine analyses, blood counts, blood chemical studies, gastric analyses, spinal fluid examinations, retinal and visual field examinations, blood pressures and x-rays of the spine and skull. It is essential that every migraine patient have a thorough eye examination by a competent ophthalmologist. This is one method of ruling out such conditions as brain tumors.

Women are affected about four times as frequently as men (see Table V). The onset of the disease is surprisingly early, as shown in Table V. There is also evidence that cyclic vomiting may be the infantile form of migraine.[34] Symptoms often lessen or disappear after the climacteric in both sexes. At this time, some patients lose their headaches, but retain the aura.

TABLE VI. DIFFERENTIAL DIAG

	INCIDENCE	AGE AT ONSET	FREQUENCY OF ATTACKS	DURATION OF ATTACKS	INTENSITY	TYPE OF PAIN
Migraine	Common	Children or young adults	2/week to one per year	Usually 12-36 hrs.	Moderate to severe	Usually pulsating
Histamine Cephalalgia	Uncommon	30-40 yrs.	Several daily or skip mos.	15 min. to few hours	Short, severe	Sharp, throbbing
Tension (Nervous)	Very common	Adults, usually	Variable; often daily	Variable	Variable, usually not severe	Dull, aching, steady may be band around head.
Sinus (Nasal)	Common	Any	May be daily	Several hrs; may be all day	Mild to moderate	Aching or drawing. Frontal in A.M. Antral in mid-aft.
Eye strain	Common	Any	May be daily	Until pt. rests eyes	Mild to moderate	Dull; follows over-use of eyes; esp. midday
Hypertension	Common	Usually 35-60	Variable, often daily	Several hours	Moderate	Dull, aching, esp. in A.M. may follow stress.
Brain tumor	Uncommon	Adults	Variable	Variable; short at first	Moderate; becomes severe	Steady dull ache; deep; worse in A.M.
Subdural Hematoma	Uncommon	Any	Becomes continuous	Steady	Becomes severe	Dull, diffuse ache; may pulsate
Temporal Arteritis	Very rare	Usually 50-70	Almost continuous	May last 1-20 months	Moderate	Throbbing at first; localized; later dull

DIFFERENTIAL DIAGNOSIS

It is important to differentiate migraine from other headaches although it may sometimes be surprisingly difficult. Table VI differentiates the common types of chronic headaches. Missing from this table are menstrual headaches, which are characterized by their occurrence only before or with the menses. True migraine occurs also at other times and in both sexes. We admit that the headaches are at times otherwise identical.

Table VI also omits acute headache such as those due to subarachnoid hemorrhage or to infectious diseases, and those syndromes with constant and typical characteristics; these include trigeminal neuralgia and sphenopalatine ganglion syndrome (''lower half headache''). In Table VI the importance of nauseas and vomiting has been minimized, since these follow any prolonged and severe head pain.

DISCOVERY OF CAUSE

The chief aim of this paper and the statistics presented is to convince physicians that every migraine patient deserves a complete allergic work-up. With cooperation and perseverance, the cause can usually be found, and the symptoms often completely relieved. Elimination diets and feeding tests can always be performed while the patient is undergoing other investigative procedures.

NOSIS OF CHRONIC HEADACHE

LOCATION OF PAIN	EYE SYMPTOMS	ASSOCIATED SIGNS AND SYMPTOMS	DIAGNOSTIC TESTS	THERAPEUTIC TESTS
Unilateral, usually	Photophobia, may have visual aura	N & V; Aura at times; G.I. symptoms with & between attacks	Induce attack by feeding test or with histamine	Gynergen. Elimination of causative foods
Unilateral, in face.	Conjunctivitis, tearing on affected side	Nasal blockage, rhinorrhea on affected side.	Histamine	Gynergen. Histamine treatment
Generalized, neck back or top head	None	Fatigue; occurs with or after stress	None	Removal from stress
Frontal or in cheeks; across bridge of nose	None	Nasal blockage; postnasal drip; sinus tenderness	Nasal smear for eosinophils; sinus X-rays	Relief by local treatment, antihistamines
Behind and in eyes	Blurring, burning, itching, tearing	Follows prolonged eye strain (close work)	Refraction	Rest; proper glasses
Usually occipital may be genl.	May be blurring	Evidence of basic disease	None	Relieve hypertension
Variable; may be unilateral or localized	May be blurring, diplopia, etc.	Depends upon site and stage of tumor	Ventriculogram, spinal tap, encephalogram, neurologic exam.	Surgery
At site of trauma. Later genl.	Usually none	History & evidence trauma; Xanthochromic spinal fluid initially	Ventriculograms, spinal tap; encephalogram	Surgery
Over artery	Diplopia, photophobia; may lead to blindness	Fever, leukocytosis; pain on chewing; artery tender distended & tortuous	Novocaine infiltration biopsy	Surgical interruption of artery

We have found feeding tests and food diaries each of equal importance in determining the food to which the patient is allergic. Food diaries rank first, because they reveal most of the minor causes of attacks. The patient should write down everything he ingests (including all ingredients) for 24 hours before each migraine. These lists are then compared to see if certain foods or groups of foods are mentioned repeatedly. These are then eliminated, later tried again to see if symptoms follow. Elimination diets used alone were helpful in 11 patients in this series.

Feeding tests are the most important method of determining allergy to major foods. The technique is as follows:

1. Place the patient on a rigid and complete elimination diet for two weeks. Exclude one major food at a time (usually milk, wheat or pork). Chocolate is eliminated throughout all diet trials.
2. After resting in the office for one-half hour, with an empty stomach, give him a feeding of the food previously eliminated, e.g.;
   A) One pint of milk, or
   B) Serving of Cream of Wheat made with water, and cane sugar, or
   C) Two cans of pure chopped pork (baby food cans).
3. If no symptoms develop, repeat the same meal one hour later and dismiss the patients with instructions to report any symptoms which may develop later.

TABLE VII. RESULTS WITH LEUKOPENIC INDEX

	MIGRAINE AFTER FEEDING	NO MIGRAINE AFTER FEEDING
WBC drop (over 1,000 cells in one hour)	8	3
WBC rise	7	8
Equivocal (drop less than 1,000)	11	10

4. If no symptoms develop, repeat with different foods, at intervals of two weeks.

If a true migraine develops following such a feeding test, it becomes obvious to the patient that this food is one major cause of his headaches. He will almost always be cooperative in eliminating that food in all forms. If he persists in having occasional attacks, less frequently than before, the offending foods can usually be tracked down by food diaries.

Skin tests were helpful in determining food allergies in only 5 cases. Because of these occasional patients, however, we regard them as an essential part of the allergic work-up. No patient should ever be dismissed as nonallergic merely because of negative skin tests. Every positive reaction to foods must be confirmed clinically, each negative regarded as merely noninformative.

Eosinophilia in the blood is a completely unreliable index of allergy in migraine patients; nor has the leukopenic index proved reliable in our hands (see Table VII). These figures are based on a drop of 1,000 cells in the white count one hour after ingestion of the suspected food. In other words, there is no reliable laboratory test for the diagnosis of food allergy. Clinical elimination and trial feedings are the only true tests for food allergy.

MANAGEMENT AND PREVENTION

The most important way to treat migraine is to prevent the attacks. No amount of medication, however effective, can replace the wonderful sense of security which a patient obtains by finding and eliminating the cause of his attacks. Table VIII shows the results we have obtained in our patients. These statistics are based upon a survey of all our private patients who fulfilled two criteria: all had classical migraine and all have cooperated with us for a period of three months or longer. This latter stipulation is based upon the two following requirements: There is a minimum period of two weeks between feeding tests, this much time being necessary to allow an adequate number of tests, if necessary. Secondly, we have no follow-up on patients who have disappeared before that time, so that we cannot judge whether or not they were really failures.

TABLE VIII. RESULTS OF ALLERGIC MANAGEMENT IN 55 PATIENTS WITH MIGRAINE

Complete Relief	35	(64%)
Marked Improvement (75% or better)	9	(16%)
Moderate Improvement (50-60% better)	2	(4%)
No relief	9	(16%)

TABLE IX. RESULTS OF TREATMENT WITH DIHYDROERGOTAMINE

AUTHOR	NUMBER OF PATIENTS	GOOD TO EXCELLENT (RESULTS IN PER CENT)
von Storch[30]	150	70-90
Friedman and Wilson[9]	36	89
Caldwell[5]	42	76
Blumenthal and Fakler[3]	51	88
Hartman[15]	20	85
Horton, Peters, and Blumenthal[17]	79	75
Pollock[24]	17	88
Charles[6]	25	88
Bercel[2]	40	87
Total	465	83

Table VIII shows that over 60 per cent of these patients found complete relief by eliminating causative foods. Another 20 per cent have been partially relieved. Altogether, over 84 per cent have found some measure of relief and almost all of these are 75 to 100 per cent better. Figures on results with psychotherapy are not easily available for comparison, but Friedman, Karron, and de Sola Pool[8] recently estimated results from psychotherapy at 66 per cent.

Of the 9 failures in this series, we feel that several could have been helped by more complete work-ups. Until recently, we did not appreciate the importance of pork as a cause of migraine. Few of these failures were ever placed on a pork-free diet. On the other hand, we far overestimated the importance of eggs; as the table shows, only two of our patients were sensitive to egg.

Contributory factors are also important and must be treated as indicated in individual cases. Formal psychotherapy is a great aid in some patients, although most will respond to the informal type easily directed by family doctors. General good health should be maintained and existing physical disabilities corrected (especially visual and endocrine).

TREATMENT OF ATTACKS

During the period while finding the cause of attacks, it is essential that the patient receive the maximum possible relief. This applies also to sporadic at-

TABLE X. RESULTS OF TREATMENT WITH CAFERGOT

AUTHOR	NUMBER OF PATIENTS	EXCELLENT	GOOD	NO RELIEF	PER CENT EXCELLENT AND GOOD
Charles, C. M.[6]	34	6	12	16	53
Cohen, S. G. & Criep, H. L.[7]	44	13	22	9	80
Friedman, L. L.[10]	28	21	2	5	82
Gotz, A.[12]	25	15	7	3	88
Hilsinger, R. L.[18]	3	0	1	2	33
Hansel, F. K.[14]	6	3	2	1	84
Horton, B. T., Ryan, R. & Reynolds, J. L.[19]	25	16	6	3	88
Kadish, A. H.[20]	30	19	7	4	87
Reeves, J. E.[26]	15	8	2	5	67
Ryan, R. E.[27]	110	81	18	11	88
Whitelaw, M. J.[31]	76	49	18	9	88
Total	396	231	97	68	83

tacks which occur later. There are two general rules for all medicines for treatment of migraine attacks:

1. Medication must be given early and in adequate doses. When the arterial walls are thickened, no medication will relax them.
2. No oral medication can be given when the patient reaches the stage of nausea as he will usually vomit them.

There is only one specific drug for migraine—ergotamine. Only two forms of ergotamine have proved consistently effective; ergotamine tartrate is the drug of choice, with Dihydroergotamine, a close second. Peculiarly, there are practically no published statistics on the efficacy of Gynergen (pure ergotamine tartrate), which is generally recognized as the most effective of all medicines for migraine when given intravenously or intramuscularly. Patients seen in attacks should be given Gynergen or Dihydroergotamine promptly, either intravenously or intramuscularly. Results of treatment with the latter as reported in the literature are shown in Table IX.

To treat future attacks, the drug of choice is Cafergot because of its ease of administration. Results reported are shown in Table X. It must be given in full doses promptly: two tablets at first sign of a headache, followed, if necessary, by two more in one hour and two more the following hour. No more than six tablets should be given for any attack, nor should this course be repeated more than twice a week. Ergot should not be used as a preventive measure (taken daily). The manufacturers have recommended that patients who have frequent migraine attacks restrict their usual coffee intake to about two cups daily in order to assure full action of the caffeine in Cafergot.

Two other methods of administering ergotamine tartrate are undergoing investigation and appear promising. These are the rectal suppositories and sublingual tablets. The tablets and suppositories used thus far have compositions similar to Cafergot. These forms deserve further investigation because they circumvent the problem of nausea.

Ergotamine has always been used cautiously, although it is used a great deal. It is to the credit of physicians and manufacturers (particularly the Sandoz Company) that there have been reported only three cases of ergotism following use of these preparations in treatment of migraine.

Because ergotamine is so specific, other measures have been largely discarded. Of the many vasoconstrictors tried, the simplest and most effective is an icebag to the head. Others used include epinephrine, pitressin, benzedrine, caffeine, pressure on carotid or temporal arteries and inhalation of 100 per cent oxygen. Results with a new preparation, Methylisooctenylamine (Octin) are encouraging, but do not compare with those for Cafergot. Nicotinic acid and testosterone have also been used recently; the latter may prove helpful in preventing premenstrual headaches.

Histamine has been used, particularly by Horton.[16] Some of our patients had received histamine previously; most of them felt worse after receiving it,

Analgesics have, of course, been used. A few patients can obtain relief from the aspirin group of drugs. In our experience, sublingual aspirin (Theryl) seems more effective than other forms.[28] Codeine is helpful in a few patients and may be used safely. The use of such narcotics as Demerol and morphine is to be condemned. Migraine is a recurring syndrome which can easily lead to addiction. Sedatives are usually disappointing as specific treatment, but mild sedation is an aid to other forms of therapy.

One important recent addition to therapy of migraine attacks is the use of intravenous calcium. Calcium gluconate seems to have a beneficial effect upon the residual headache, apparently due to muscle spasm, which accompanies migraine and other types of long-standing headaches. We have recently used a 20 per cent solution of calcium gluconate intravenously in these cases, with rather striking results. It is given slowly and followed by a small amount of intravenous ergotamine tartrate.

Surgical measures of various types have been used, but the results are not commensurate with the discomfort and risk involved.

SUMMARY

1. In a group of 55 patients with classical migraine who have been followed for a minimum of three months, 80 per cent have been either completely or almost completely relieved of attacks by detection and elimination of the causative foods.

2. Allergy to foods is the prime precipitating cause of attacks. Statistics are presented to show the relative frequency of various foods. Chocolate is the most important cause, followed by milk, wheat, and pork.

3. A discussion is presented of the diagnosis, differential diagnosis, mechanism, and treatment of attacks of migraine.

4. It is concluded that migraine is basically an allergic disease, although psychic stimuli may provoke individual attacks in allergic individuals.

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QUANTITATIVE STUDIES IN SKIN TESTING

V. The Whealing Reactions of Histamine and Ragweed Pollen Extract

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IT WAS propounded in 1927, by Lewis,[1] that histamine is of importance in the mediation of the immediate-wheal type of response in human skin. He showed that the reaction of skin to intradermally injected histamine is a triple response. First seen is a local red reaction caused by local arteriolar dilatation. Next to be observed is the surrounding red flare, mediated by an axon reflex. Finally there appears a pale, firm, sharply demarcated, round or oval wheal, caused by the extravasation of fluid and plasma protein through the hyperpermeable capillary wall.

Lewis showed that this triple response is seen whenever the skin comes in contact with any of a wide variety of noxious stimuli of intermediate intensity—heat, cold, stroking, peptone, nettle stings, etc. He postulated that each of these agents is capable of causing the tissues to release histamine or some histamine-like substance.

The specific allergic skin responses differ from the whealing caused by heat, cold, stroking, etc., in that an antigen-antibody reaction is involved. Only those subjects who harbor the specific antibody show the triple response when exposed to a given antigen.

Katz[2] in 1942 proved that histamine is actually released during the cutaneous reaction to specific antigens. He demonstrated that the amine is present in the exudate of a blister after the injection of an antigen to which the subject is sensitive. Nilzen[3] showed that after whealing caused by mechanical stimulation there is a decrease in the amount of extractable histamine in the skin.

Nilzen also studied the blood levels of extractable histamine in patients suffering from chronic urticaria. He found that the level is low during acute attacks and rises during recovery. The probable explanation for this finding lies in the work of Dragstedt[4] who showed that free histamine disappears rapidly from the blood. Rosenthal and Tabor[5] and more recently Urbach[6] have shown that the amine is conjugated to form acetyl histamine, 4 (beta-acetyl aminoethyl) imidazole, which is excreted in the urine.

The evidence that histamine is released during the cutaneous whealing reaction is convincing, but there remains the question of whether it is the only pharmacologically-active substance involved in the reaction. This is a question which will be considered later in the light of the present investigation.

This study was made possible by the financial assistance of Parke, Davis & Company, Detroit.

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The work of Schloss,[7] Alexander, Harter, and McConnel,[8] Bowman,[9] and, more recently, Becker and Rappaport[10] has shown that differences exist in the skin sensitivity to allergens at different sites, and, moreover, that these differences follow a regular pattern. For instance, Becker and Rappaport examined the forearms of ragweed-sensitive subjects and found that constant doses of antigen cause larger wheals on the ulnar aspect than on the radial aspect. Likewise sites near the cubital fossa are more reactive than sites near the wrist.

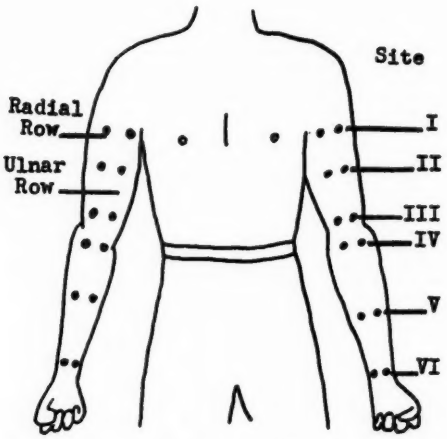

Fig. 1.—Position of injection sites for histamine on arm and forearm.

Differences in site sensitivity are open to at least two different interpretations: it is possible that the antigen causes the release of different amounts of histamine at different sites, or there may be a difference in the whealing activity of the skin at the various sites to rather constant amounts of released histamine. Bowman[9] and, more recently, Wiseman[11] believed that they could demonstrate a difference between the site-response to histamine and the site response to a specific allergen. This evidence would favor the former alternative. The present authors examined the site-response of the skin of the upper extremity to constant doses of histamine, and compared the results with the site-response to constant doses of ragweed pollen extract, as determined by Becker and Rappaport.

To determine whether or not other substances besides histamine are active in mediating the allergic wheal reaction, the investigators studied the effect of dosage upon wheal diameter. The dose-response curve for histamine was determined, and this was compared with the dose-response curve obtained by Becker and Rappaport for ragweed extract. It was noted that the curves for histamine and the specific antigen are of the same general type. Therefore appropriate subjects were tested simultaneously with graded doses of both histamine and ragweed pollen extract.

There is a large amount of variation encountered in skin testing. The data therefore were submitted to statistical analysis to measure the various factors

affecting wheal diameter and to determine the accuracy of the techniques employed.

METHODS AND RESULTS

Part I. Histamine Site-Response.

Subjects: A group of 23 adult human volunteers were chosen without regard to age, sex, race, or ragweed sensitivity.

Solution: Crystalline histamine dihydrochloride (Hoffmann LaRoche) was dissolved in distilled water containing sufficient sodium hydroxide to render the solution neutral (pH 6.5 to 7.0), and sufficient sodium chloride to make it isotonic. The solution was sterilized by passage through a Seitz filter. In strength it contained one part of free histamine base per 10,000 parts of solution. A fresh solution was prepared for each day's injections.

Sites: Six radial and six ulnar sites were tested on the flexor aspect of each upper extremity. The sites in each row were numbered from proximal to distal,

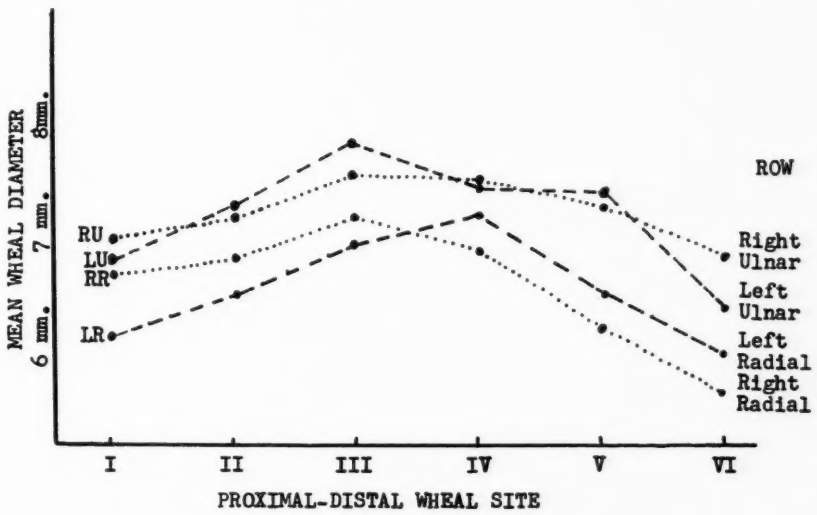

Fig. 2.—The change of responsiveness to histamine with the position of the injection site on arm and forearm.

as shown in Fig. 1, and were located as follows: I, 2 cm. below insertion of pectoralis major muscle; II, midway between I and III; III, 1.5 cm. above cubital crease; IV, 2.5 cm. below cubital crease; V, midway between IV and VI; VI, 2 cm. above proximal carpal crease.

Technique: The histamine solution was injected at the 24 sites with a 1 c.c. syringe and a No. 27 short-bevel needle. The needle tip was placed into the corium of the skin, and the solution was injected so as to produce a bleb approximately 2 mm. in diameter. After 15 minutes the diameters of the resultant wheals were measured with vernier calipers to tenths of millimeters. In the case of oval wheals, the longer diameter was measured. Pseudopods on wheals were excluded from measurement. The results of the 24 tests on each of 23 subjects were plotted and submitted to an analysis of variance,[12] con-

TABLE I

SOURCE OF VARIANCE	D.F.	SUM OF SQUARES	MEAN SQUARE	F	(1% F)	P
Subjects	22	205.18	9.32	11.9	(1.88)	$< 1\%$
Positions	5	77.11	15.42	19.7	(3.06)	$< 1\%$
Rad. vs. Ul.	1	53.54	53.54	68.3	(6.70)	$< 1\%$
Left vs. Rt.	1	0.06	0.06	0.07	(6.70)	$> 5\%$
1st Order Interactions	165	146.15	0.88	1.14	(1.32)	$> 5\%$
Error	357	280.03	0.78			
Total	551	762.07				

sidering as sources of variation (a) subjects, (b) positions I to VI, (c) radial vs. ulnar aspect, and (d) right vs. left extremity. The error term in the analysis of variance was considered a measure of the accuracy of the technique.

Results: The mean wheal diameters at the 24 sites are shown in Fig. 2. A summary of the analysis of variance of the data is shown in Table I.

Fig. 2 and Table I taken together indicate that:

1. Individuals differ significantly in their reactivity to histamine, as would be expected.

2. There is a statistically significant difference among the six sites in each row, those sites at the cubital region being most reactive to histamine, and those at the wrist least reactive.

3. Sites in the ulnar rows are significantly more reactive than corresponding sites in radial rows.

4. There is no significant difference between corresponding sites on the left and right extremities.

5. These four sources of variation are relatively independent of one another in their effects upon the mean wheal diameter, as is shown by the insignificant value for F for the first order interactions.

The sources of variation studied here for histamine showed a pattern similar to that of corresponding sources of variation when Becker and Rappaport studied the site differences in the whealing of ragweed pollen extract.

Part II. Histamine Dose-Response.

Subjects: A group of 54 human volunteers from the out-patient population of the University of Illinois Allergy Clinic were employed in this portion of the investigation. They were chosen without regard for age, sex, race, type of allergic complaint, or specific sensitivity, with the exception that subjects under ten years of age were avoided.

TABLE II

	SUBJECT 1 RIGHT ARM	NO. 1 LEFT	NO. 2 RIGHT	NO. 2 LEFT	NO. 3 RIGHT	NO. 3 LEFT
I	D	A	C	F	E	B
II	F	E	A	B	D	C
III	C	B	F	D	A	E
IV	A	D	E	C	B	F
V	B	C	D	E	F	A
VI	E	F	B	A	G	D

Solutions: A stock solution of histamine dihydrochloride was prepared to be sterile, isotonic, neutral in reaction (pH 6.5-7.0), and in strength one part free histamine base per 100 parts of solution. Successive quartile dilutions were prepared from this stock solution by serial passage of 1 c.c. of solution into 3 c.c. of sterile isotonic saline. The six solutions so prepared had strengths as follows:

A, 0.01 (stock solution)	D, 0.000156
B, 0.0025	E, 0.000039
C, 0.000625	F, 0.0000096

Sites: Six sites were employed on each upper extremity of the subjects in the dose-response determinations. These six sites were located in a line along the mid-flexural surface of the extremity, as indicated in Fig. 3. The six dilutions of histamine were distributed among the six sites by means of a Latin square randomization, so that site differences might be eliminated. A different column of the Latin square was used for each extremity, and a new square was generated from a table of random digits for each three subjects (each six extremities). A sample Latin square is shown in Table II.

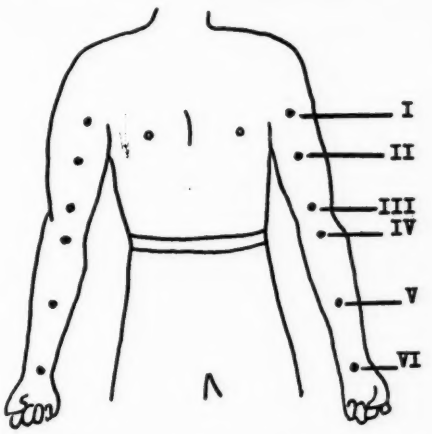

Fig. 3.—Position of injection sites for ragweed on arm and forearm.

Technique: The six dilutions of histamine were placed in six syringes fitted with No. 27 short-bevel needles. The dilutions were injected intradermally at the indicated sites, and after fifteen minutes the longest diameters of the resultant wheals were measured. The mean wheal diameter for each dilution was calculated, and the results were plotted.

Results: Fig. 4 is a semilogarithmic plot of the mean wheal diameter against the logarithm of the concentration of histamine injected. The equation for the best straight line through these points is

$$Y = 2.51\ X + 18.65$$

where Y is the mean wheal diameter and X is the logarithm of the histamine concentration. The standard error of the observed points from this equation is 0.299 mm.

Fig. 5 is a log-log plot of the mean wheal diameter logarithm against the histamine concentration logarithm. The equation for the best straight line through these points is

$$Y = 0.1131\ X - 1.3742$$

where both X and Y are logarithms. The standard error of the observed values from this equation is 0.255 mm. Comparing this standard error with the value of 0.299 mm. for the semilog plot, it is apparent that the fit of points to one plot is not remarkably better than to the other.

Becker and Rappaport found that their ragweed data could be fitted to a dose-response curve of this log-log type. Thus the two substances appear to behave in the same general manner under the transformation of dose response. In order to test more rigidly the similarity between the dose-response curves, the technique was repeated, measuring the response to both histamine and ragweed extract in the same subjects at the same time.

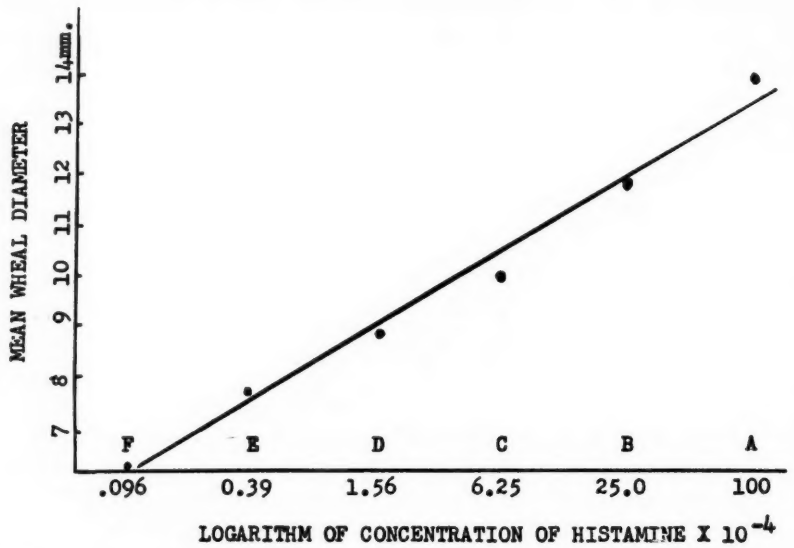

Fig. 4.—The relationship between the logarithm of histamine concentration and mean wheal diameter.

Part III. Histamine-Ragweed Dose-Response Comparison.

Subjects: A group of 24 volunteers from the University of Illinois Allergy Clinic were used in this portion of the project. Of necessity, all subjects were ragweed-sensitive.

Solutions: The histamine solutions employed were identical to those used in Part II. The ragweed solutions were prepared by quartile dilution from a stock solution of 10 per cent aqueous ragweed pollen extract which contained 1.5 mg. of nitrogen per c.c. The resultant solutions were sterile, isotonic, neutral in reaction, and had strengths as follows:

Stock, 0.10 (not injected)
O, 0.025 (not injected)
A, 0.00625
B, 0.00156
C, 0.00039
D, 0.000096
E, 0.000024
F, 0.000006

Sites: The sites used were the same as in Part II.

Technique: Each subject received injections of ragweed extract in one extremity and injections of histamine in the other. The solutions were alternated from right to left and left to right extremities on consecutive subjects. A Latin square was used to randomize the injection sites. The same pattern was used for both histamine and ragweed injections in a given subject so that he received corresponding doses at corresponding sites on the two extremities. A new Latin square was generated for each six subjects.

The diameter of each histamine wheal was plotted against the diameter of the corresponding ragweed wheal. On the same plot, the mean diameter for each of the six histamine dilutions was plotted against the corresponding ragweed dilution mean diameter.

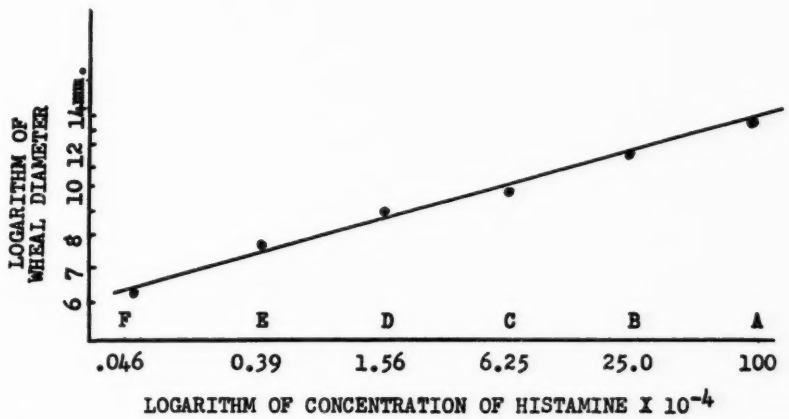

Fig. 5.—The relationship between the logarithm of histamine concentration and logarithm of wheal diameter.

Results: Fig. 6 shows the diameter of each of 144 histamine wheals plotted against the diameter of the corresponding ragweed wheal. Also shown are the mean values for the six dilutions employed. The straight line whose slope = 1 represents a theoretical axis upon which all points would fall if ragweed = histamine and the data were collected without error.

From Fig. 6 we see that:

1. Mean values for the six dilutions closely approximate the theoretical axis.
2. Individual values show considerable variation. (The coefficient of correlation, r, for the array is + 0.589.)

The lack of perfect correlation may be caused by the variability of response to the liberated histamine or may have its explanation in the liberation of some substance other than histamine which is at least in part responsible for the whealing reaction. By the statistical technique of analysis of covariance we can test the hypothesis that the variation in the histamine wheal diameters is sufficiently large to account for the variation seen in the ragweed wheal diameters. Table III is a summary of the analysis of covariance of these data.

TABLE III

SOURCE OF VARIATION	D.F.	Sh^2	Shr	Sr^2	SUM OF SQUARES	D.F.	MEAN SQUARE
Total	143	2744.85	1693.46	3007.47	1962.68	142	
Dilutions	5	1207.10	1049.53	866.48			
Error	138	1537.75	643.93	2140.99	1871.35	137	13.66
					91.33	5	18.26

$F = 18.26/13.66 = 1.34$
(5% F = 2.88)
P >5%

The small value for F indicates that there is no significant difference between the behavior of the two substances. The answer to the statistical question is, "Yes, the variation in the histamine data is sufficient to account for the variation encountered in the ragweed data." Within the limits of the techniques employed, there is no apparent need to postulate the existence of wheal-mediating substances other than histamine.

DISCUSSION

The results obtained in this study must be viewed in the light of the several serious limitations inherent in the quantitative skin testing procedures employed. First is the large amount of variation encountered in the data. To a considerable extent this variation arises from the mechanical difficulty of injecting a small constant amount of solution to a constant depth into the skin.

A second limitation is the flatness of the dose-response curve. As the concentration of whealing agent is increased 1,000 times, the wheal diameter increases by a factor of two. This means that wheal diameter is not a particularly sensitive tool for measuring amounts of apparent histamine.

The third limitation of the method is the narrow range over which wheal diameters can be studied accurately. Wheals less than 4 mm. in diameter are difficult to measure precisely. Wheals larger than 12 or 15 mm. in diameter are prone to develop pseudopods, and this introduces an additional source of error. Furthermore, with higher concentrations of a specific antigen there is an increasing chance of inducing a constitutional reaction in the subject. It is altogether possible that certain differences, now hidden, would become apparent if the range of study could be extended. As Clark[13] has pointed out, curves of radically different types may be indistinguishable if viewed over narrow ranges only.

The limitations imposed by the narrow range of study and the flatness of the dose-response curve make it especially important that the variation caused by mechanical factors such as injection technique be reduced to an absolute minimum. This was attempted by the use of statistical analysis on samples containing a large number of individuals.

These statistical techniques relate the magnitude of observed differences to the magnitude of the standard error of the method. With a smaller standard error, finer differences can be detected. Since standard error is an inverse function of the square root of the number of items in the sample, standard error can be made smaller by employing larger samples. But to thus increase the accuracy

of the present investigation by any significant amount would require prohibitively large samples. For example, to increase by a factor of ten the accuracy of Part I of this study would require a sample of 55,200 skin wheals.

Within the limits of the techniques employed, the site response to ragweed pollen extract in ragweed-sensitive subjects and the site response to histamine were indistinguishable. The same differences in site reactivity which Becker and Rappaport[10] showed in their ragweed studies were found in this study of histamine. Not only is there a qualitative similarity, but to a certain extent there is a quantitative parallelism as well. Becker and Rappaport found that the decreased reactivity of the radial aspect as compared with the ulnar aspect was equivalent to a 50 per cent decrease in the strength of the solution employed. In this histamine study, the corresponding decrease in reactivity was equivalent to a 43 per cent weaker solution.

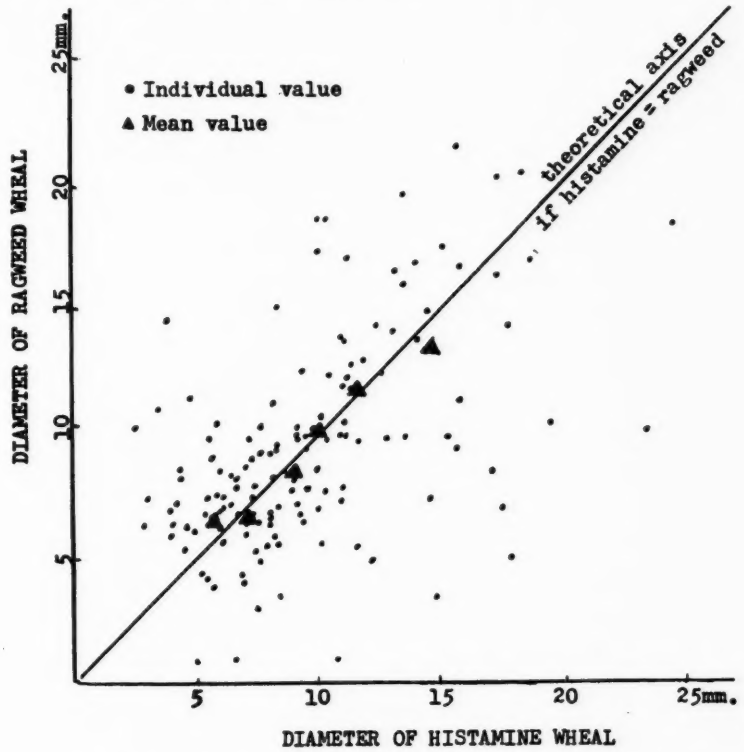

Fig. 6.—The relationship between histamine and ragweed response.

In the ragweed study Site VI was less reactive than Site IV by an amount equivalent to a 55 per cent decrease in solution strength. In this study the site reactivity decrease from IV to VI was equivalent to a 60 per cent weaker solution.

Thus we conclude that since the same site differences are found to histamine as to ragweed injection that the antigen-antibody portion of the wheal mechanism is not implicated in the site difference but rather that it

must be inherent in the differences of the skin itself. We believe that there is a difference in the whealing activity of the skin at various sites to rather constant amounts of released histamine.

Our conclusions are at variance with the findings of Bowman[9] and more recently Wiseman.[11] Wiseman stated, "The author was able to confirm the findings of Bowman who showed that responsiveness to histamine increased as tests were introduced progressively down the arm, whereas responsiveness to atopens diminished under the same circumstances."

We must point out that in studies involving small numbers of individuals, apparent differences must be very large to be significant. We can, of course, say nothing concerning Wiseman's conclusions as to the relative hyperactivity of the crease area since that area was not tested in our work.

In Part III of this study, the dose-response curves of histamine and ragweed extract were compared. The mean difference between histamine and ragweed wheal diameters is of little interest because the experiment was so designed that this mean difference was as close to zero as possible. Of greater interest is the question of whether there is in the ragweed data a component of variation not present in the histamine data. If such an additional component were present, it would suggest the presence of additional whealing substances. When the technique of analysis of co-variance was used to answer this question, no such component was found.

Thus the findings of this study lend support to the idea that histamine is the mediating substance in the cutaneous whealing caused by a specific antigen in appropriately sensitive subjects. From these findings there is no evidence that there are other pharmacologically-active substances mediating the reaction. But the error of the method is sufficiently large that the presence of other active agents cannot be definitely excluded. All that can be said of them is that if they are present, their effect is small with respect to the error of the measuring procedure.

SUMMARY

1. Variations in the site response to constant doses of intradermally injected histamine were observed. These differences closely paralleled those seen previously in the site response of ragweed-sensitive subjects to intradermally injected ragweed pollen extract.

2. It is concluded that the antigen-antibody portion of the wheal mechanism is not implicated in the site differences, but rather it must be inherent in the differences of the skin itself.

3. Within the range studied, the dose response of histamine approaches linearity on both logarithmic and semi-logarithmic plots.

4. The variation seen in the histamine dose-response data is sufficient to account for the variation encountered in the ragweed dose-response data.

5. Within the limits of the techniques employed, there is no evidence that there are other active substances besides histamine mediating the cutaneous whealing reaction induced by a specific antigen.

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RAGWEED INVASION OF OREGON

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PORTLAND, OREGON

THE unique absence of ragweed from the Pacific Northwest has been of interest to aerobiologists as well as to the ragweed hay fever sufferers who have sought refuge and often permanent residence here. It has been a source of wonder that the fertile, highly cultivated valleys west of the Cascade Mountains have remained free of this weed, which is indigenous to most of the North American continent. Even in these past several decades, with extensive cross-continental travel, this area remained apparently free from invasion by seeds of ragweed plants other than the occasional ones found growing along the railroad tracks. In the past, the periodic report of large areas infested with this weed would invariably prove to be a case of mistaken identity.

Several years ago, isolated pollen grains of ragweed were found on the slides placed on the roof of the Medical-Dental Building in the metropolitan center of Portland. This prompted field surveys, which, with the aid of the County Agent, revealed a large acreage in the adjoining Clackamas County overrun by common short ragweed. This contaminated area was so sharply delineated that it seemed to have been planted. In fact, an apocryphal story suggested that an Iowa farmer, who came there many years ago to homestead that piece of land, brought with him some small grain contaminated by the seed of the ragweed, and the latter has flourished in its confines long after the original farmer departed in discouragement.

In the past decade, the state of Oregon has had a population increase of over 35 per cent. Most of this influx was from other states where ragweed flourishes, and some of these new arrivals came specifically to get away from the cause of their yearly affliction. A number were pleasantly surprised to be so well in August and September. To the newcomer from the middle west and east, the sight of a roadside overgrown with this short ragweed was too familiar to provoke any real interest. To the native, these weeds and their implications were so entirely foreign that they apparently remained unnoticed for several years.

Yet, a good deal of interest was aroused, in 1949, over this discovery, and although a certain amount of inertia and divided responsibility among government agencies prevented the establishment of a program of control, the newspapers civic organizations and leaders, and a number of refugees from midwest and eastern ragweed hay fever seasons, contributed time and funds to begin such a program of weed eradication. In late July of 1950, several weed control methods were applied to the original area. Mr. Frank G. Mackaness, Agriculture Consultant for Portland General Electric Company, was invaluable in his efforts, and the following are his observations.

"From the experience we have had with ragweed (*Ambrosia artemisiaefolia*) in this region I should say that it falls into that group of plants which is

Received for publication, April 8, 1952.

Fig. 1.—Spraying truck showing boom mounted with Monarch Nozzles attached.

Fig. 2.—Grassland showing no ragweed plants in 1951, which was heavily infested in 1950, but was thoroughly sprayed with the sodium salt of 2,4-D 95 per cent.

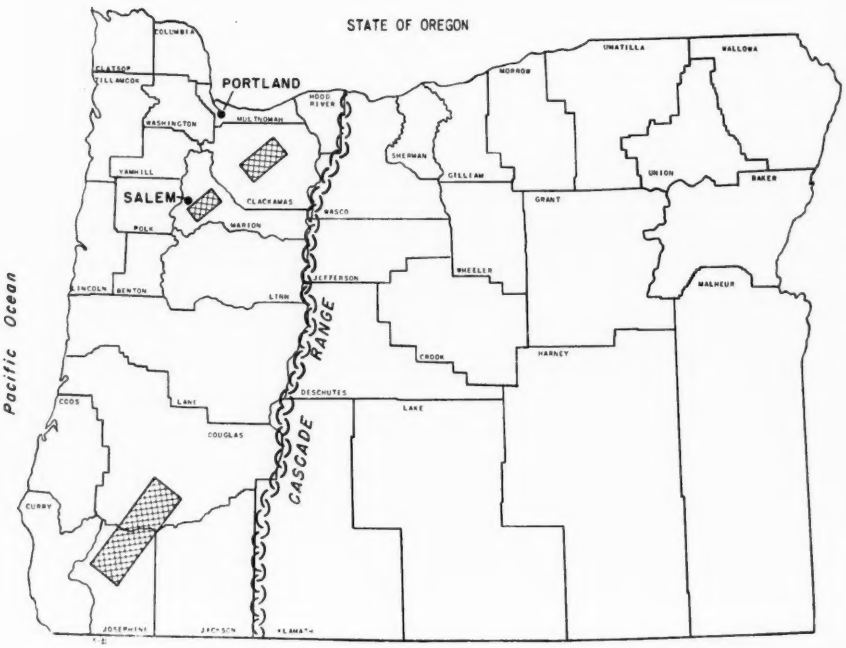

Fig. 3.—Areas where ragweed was found or reported to exist are shown by cross-hatch.

Fig. 4.—A barley field near Salem, Oregon, overgrown with ragweed.

Fig. 5.—A single swath of ragweed in a drainage ditch near Salem, Oregon.

Fig. 6.—A close-up view of a robust ragweed plant found among those seen in Fig. 5.

very easily killed by 2,4-D and related chemicals. Plants of all ages from the smallest seedling to the mature fruiting plant appear to be equally susceptible and I have reason to believe that spraying dormant seeds renders them inviable.

"Of the several types of spray tried in 1950 on the McComas farm, one gave incomparably better results than the others. This was a Chipman Chemical formulation of the Sodium Salt of 2,4-D 95%, which they no longer manufacture. It is a relatively insoluble material in any but very dilute concentrations. We mixed 20 lbs. of the powder in 200 gallons of water in a sprayer fitted with extra agitators achieving thereby a dispersion rather than a solution. This was then applied through a conventional boom mounted 24″ above the ground with Monarch Nozzles, type F 96, having orifices of 67/1000″ spaced every 18 inches [Fig. 1]. A pressure of 200 pounds was maintained, the rig travelled 7 miles per hour and covered about 5 acres with the 200 gallons.

"The immediate kill on visible ragweed was the same in all cases whether the 2,4-D was applied as an amine, sodium salt or isopropyl ester, but the sodium salt described above either had sufficient residual effect to kill seedlings as they germinated or it penetrated the ground sufficiently to render inviable seeds near the surface. At any rate, upon inspection in the summer of 1951, this formerly infested field had ragweed plants only on the mole hills [Fig. 2].

"There is one brighter side to the problem. In the areas where the weed has been reported in the Willamette Valley, grassland farming would be as profitable or more profitable than the indifferent catch crops presently raised. Managed grass land coupled with regularly repeated spraying to catch the seedlings as they emerge from the vast amount of buried seed seems to offer the greatest likelihood for ultimate eradication."

The well-publicized activities in eradication of one ragweed patch provoked reports of infestations in adjoining Marion County, and in Douglas and southernmost Josephine Counties—all west of the Cascade Range. (Fig. 3.) In Marion County, and particularly in the outskirts of the capital city of Salem, this infestation has become quite extensive, especially along the roadsides, railroad tracks, and in adjoining grain fields. (Fig. 4.) There is, therefore, a real threat to the entire, extensive, highly cultivated Willamette Valley, which is one of the most productive and the most highly populated areas of the state.

We do not know how long this infestation has been reseeding its confines. Samples of soil at various depths for viable ragweed seeds would be informative. It is reasonable to believe from the finding of seedlings on mounds made by rodents that the seeds might be found at a considerable depth and may remain viable for a number of years. Such conjectures must lead to well-organized responsibility for control of the present infestations and constant vigilance for new areas of ragweed invasion.

SUMMARY AND CONCLUSIONS

1. Common ragweed has finally invaded the Pacific Northwest which has, in the past, boasted freedom from this hay fever-producing plant.

2. The atmospheric pollen count, even in close proximity to the contaminated areas, is minimal and no clinical hay fever due to ragweed has yet been reported.

3. With the population increase, many thousand former ragweed sufferers are now living in this area. With our mild weather, the local pollen season may extend from February to November, rather than ending, as it does now, in July.

4. Effectiveness of certain methods of eradication have been reported and methods of further control have been suggested.

5. Present problem of control of this infestation of ragweed would be inexpensive and relatively easy.

6. The American Academy of Allergy could, through positive interest, contribute a great deal in arousing concern and a sense of responsibility on the part of civic organizations, governmental agencies, railroads and the Highway Commission and local boards of health to act promptly and maintain a constant vigilance in keeping ragweed, at least "clinically," out of the Pacific Northwest.

HEADACHE STUDIES. STATISTICAL DATA. II. HEADACHE PATTERNS

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RECENTLY the incidence of headache in 4,634 individuals was reported.[1] It had been recognized that no large scale, statistical studies of headache were available. The previous report described in detail the method used in the survey. Briefly, this was the procedure followed.

A standard questionnaire was devised and employed throughout the study. After the questionnaires had been filled out, the findings were transposed to IBM cards so that calculations and computations could be made on virtually any combination or relationship desired. It is important to emphasize that a cross-section survey was made, and throughout the study, 95 per cent cooperation was deemed essential for a participating group to be included in the final data. This would obviate the faulty basis that would be established by purely random sampling.

In Group I, the questionnaire was distributed to 3,589 hospital employees from three separate hospitals. Assistance was given by the department heads, when necessary. Those submitting incorrectly or incompletely filled out forms were assisted on an individual basis to minimize error. Of the groups surveyed, this group more closely approximated the general population.

In Group II, several diverse categories of individuals, homogenous within each category, were surveyed in blocks of 100 each. This comprised housewives, salesmen, saleswomen, white manual laborers, and Negro manual laborers. In this portion of the study, trained interviewers directly asked the questions and recorded the answers.

In Group III, the questionnaires were distributed to 544 individuals whose intelligence was sufficiently high to ensure reasonably accurate data. This again included homogenous categories which were as follows: freshmen medical students, senior medical students, practicing male physicians, white Catholic Sisters, and Negro Catholic Sisters.

Group IV was simply the total of Groups I, II, and III.

It was seen that comparable findings in different groups adequately paralleled each other in almost all instances. This fact indicates that each of the methods of study provided reliable data.

All groups were divided into headache and nonheadache fractions. This permitted study of the background factors in each fraction.

This work was made possible by a grant from Sandoz Pharmaceuticals to the L. S. U. School of Medicine.

Presented in part at the Annual Meeting of the American Academy of Allergy in New York City, Feb. 5, 1951.

From the Department of Medicine, Louisiana State University School of Medicine.

Received for publication, Feb. 4, 1952.

Much of the important data were found to be statistically significant by Dr. Huldah Bancroft, Professor of Biostatistics, Tulane University School of Medicine.

The size of the groups and the number of those with headache in each group are listed in the following table:

TABLE I

	I	II	III	IV (TOTAL)
No. of entire group	3589	501	544	4634
No. of headache fraction	2380	205	420	3005

The IBM analysis provided a method of determining reasonably accurately the percentage distribution of certain recognized headache patterns. The diagnostic criteria defining each of these patterns were chosen to conform as closely as possible with concepts generally accepted by headache authorities.

MIGRAINE

We first set up certain arbitrary criteria for migraine based specifically on the symptomatology of the headache attack itself, and on the recognized hereditary tendency.

1. Unilateral or bilateral location on the sides of the head
2. Gastrointestinal distress
3. Hereditary history of headache
4. Prodromal symptoms
5. Throbbing type of headache

In Group I, out of 2,380 cases of headache (the headache fraction), only 0.4 per cent checked all five criteria, 2.8 per cent checked any four criteria, 11.0 per cent checked any three criteria, and an additional 0.9 per cent checked one and two only. This gave a total per cent for migraine in Group I of 11.9. It is apparent that we included any individual with any type of headache that even remotely resembled migraine.

Similar data for the headache fractions of all four groups are as follows.

TABLE II

	I	II	III	IV (TOTAL)
All 5 criteria	0.4	0.5	1.7	0.6
Any 4 criteria	2.8	3.9	6.7	3.4
Any 3 criteria	11.0	15.6	18.8	12.4
Criteria 1 and 2 only	0.9	0.5	0.5	0.8
Total % of headache fraction	11.9	16.1	19.3	13.2
Total % of entire group	7.9	6.6	14.9	8.6

Realizing that this classification is quite broad, additional requirements were delineated. In order for a case to be considered migrainous, any four of the criteria would have to be answered affirmatively, or three would be acceptable if criteria one and two were specifically included.

The percentage fulfilling these latter requirements in the four groups is as follows.

	I	II	III	IV (TOTAL)
Per cent of headache fraction	4.6	4.4	8.8	5.2
Per cent of entire group	3.0	1.8	6.8	3.3

Therefore it may be seen that migraine (when broadly defined) exists in 13.2 per cent of all cases of headache, or in 8.6 per cent of the general population. When migraine is more rigidly defined it is seen to occur in 3.3 per cent of the general population, or in 5.2 per cent of all headaches.

Fig. 1 graphically illustrates the basis for these observations. Using this figure, other variations of the definition of migraine may be set up. As an example, the criteria of unilateral or bilateral pain may be disregarded and migraine might be redefined. The percentages of those individuals in the headache fractions answering affirmatively Criteria Nos. 2, 4, and 5 are as follows.

I	II	III	IV (TOTAL)
3.9	6.8	5.7	4.3

The percentages of those answering affirmatively Criteria Nos. 2 and 5 are as follows.

I	II	III	IV (TOTAL)
10.5	12.7	15.2	11.4

Although the author feels that a headache may be vascular even if no throbbing exists, others may hold the opinion that throbbing is the main feature to be considered in defining a vascular type of headache. The throbbing type of headache (Criterion No. 5) is found in the following per cents in the headache fractions of the four groups.

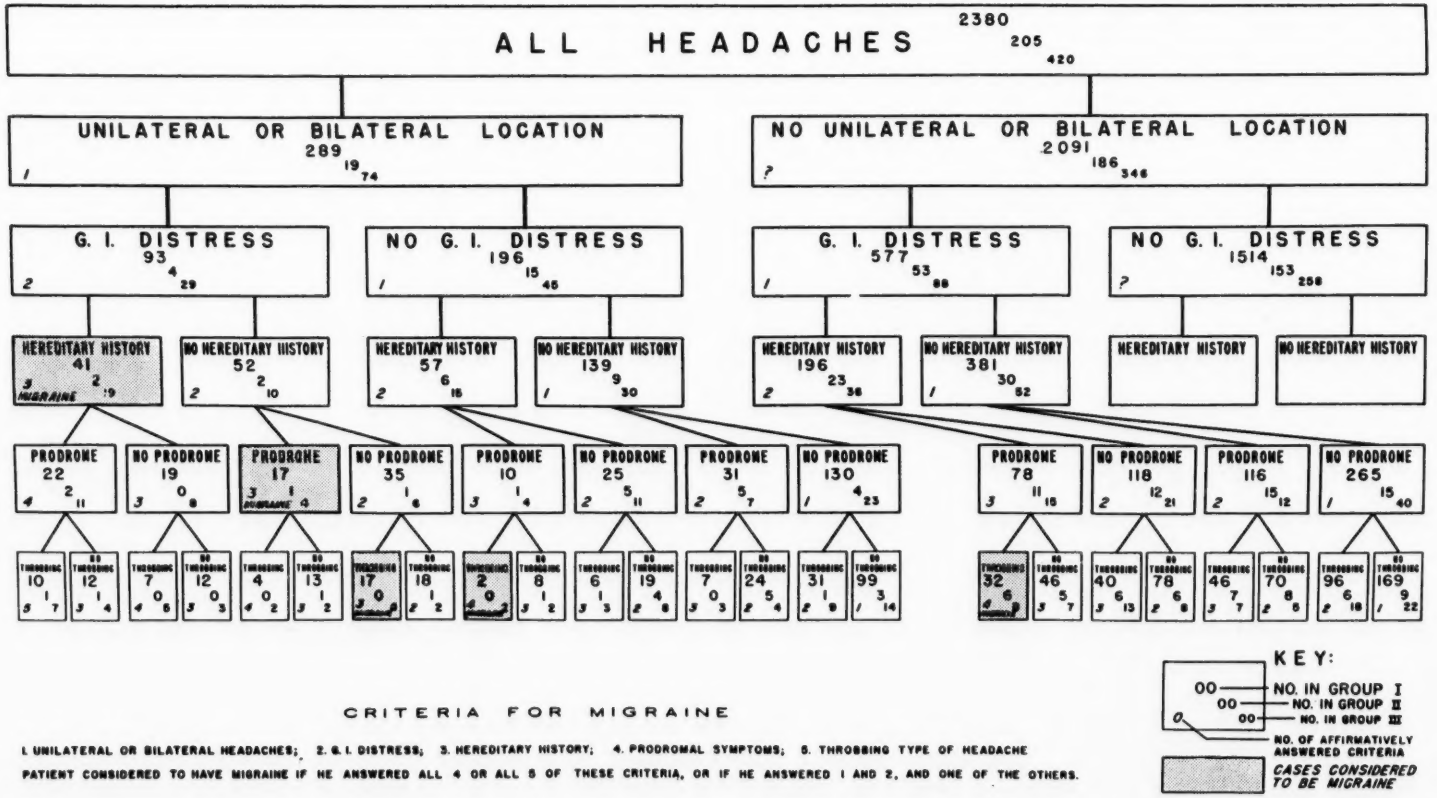
I	II	III	IV (TOTAL)
28.6	31.7	35.5	29.8

The percentage of those who complained of gastrointestinal distress (Criterion No. 2) are as follows.

I	II	III	IV (TOTAL)
28.1	27.8	27.9	28.1

It is obvious that there are many types of vascular headache which may be classified as atypical migraine, or rather as "vascular headache variants." It may be proper to distinguish the latter from "migraine variants," which may exist even in the absence of actual headache.

MIGRAINE SYMPTOMS


ALL HEADACHES 2380 205 420
UNILATERAL OR BILATERAL LOCATION 289 19 74
NO UNILATERAL OR BILATERAL LOCATION 2091 186 346
G. I. DISTRESS 93 4 29
NO G. I. DISTRESS 196 15 45
G. I. DISTRESS 577 53 88
NO G. I. DISTRESS 1514 153 258
HEREDITARY HISTORY 41 2 19
NO HEREDITARY HISTORY 52 2 10
HEREDITARY HISTORY 57 6 15
NO HEREDITARY HISTORY 139 9 30
HEREDITARY HISTORY 196 23 36
NO HEREDITARY HISTORY 381 30 52
HEREDITARY HISTORY
NO HEREDITARY HISTORY
PRODROME 22 2 11
NO PRODROME 19 0 8
PRODROME 17 1 4
NO PRODROME 35 1 6
PRODROME 10 1 4
NO PRODROME 25 5 11
PRODROME 31 5 7
NO PRODROME 130 4 23
PRODROME 78 11 15
NO PRODROME 118 12 21
PRODROME 116 15 12
NO PRODROME 265 15 40
THROBBING 10 1 7
NO THROBBING 12 1 4
THROBBING 7 0 6
NO THROBBING 12 0 3
THROBBING 4 0 2
NO THROBBING 13 1 2
THROBBING 17 0 2
NO THROBBING 18 1 2
THROBBING 2 0 2
NO THROBBING 8 1 2
THROBBING 6 1 3
NO THROBBING 19 4 8
THROBBING 7 0 3
NO THROBBING 24 5 4
THROBBING 31 1 9
NO THROBBING 99 3 14
THROBBING 32 6 9
NO THROBBING 46 5 7
THROBBING 40 6 13
NO THROBBING 78 6 8
THROBBING 46 7 7
NO THROBBING 70 8 6
THROBBING 96 6 18
NO THROBBING 169 9 22
KEY:
00 NO. IN GROUP I
00 NO. IN GROUP II
00 NO. IN GROUP III
0 NO. OF AFFIRMATIVELY ANSWERED CRITERIA
CASES CONSIDERED TO BE MIGRAINE

CRITERIA FOR MIGRAINE

1. UNILATERAL OR BILATERAL HEADACHES; 2. G. I. DISTRESS; 3. HEREDITARY HISTORY; 4. PRODROMAL SYMPTOMS; 5. THROBBING TYPE OF HEADACHE

PATIENT CONSIDERED TO HAVE MIGRAINE IF HE ANSWERED ALL 4 OR ALL 5 OF THESE CRITERIA, OR IF HE ANSWERED 1 AND 2, AND ONE OF THE OTHERS.

Fig. 1.

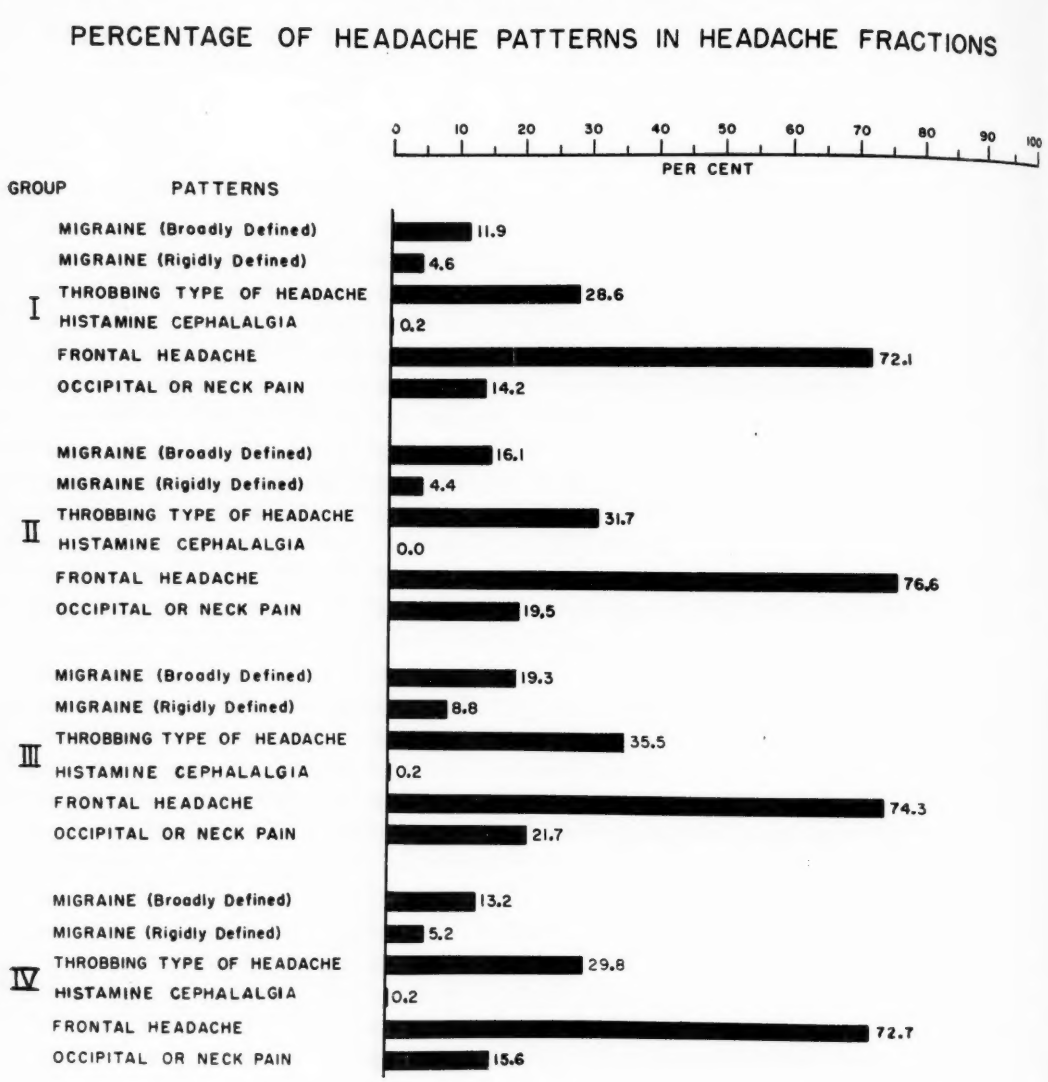


Fig. 2.

HISTAMINE CEPHALALGIA

We then set up eight arbitrary criteria for (Histamine Cephalalgia):

1. Unilateral pain
2. No prodromal symptoms
3. Visual disturbance
4. No vomiting
5. Timing, or characteristic appearance during sleep
6. Rhinorrhea or neck pains*
7. Less than one hour duration
8. Of a constant type

*Criterion No. 6 consisted of rhinorrhea or neck pains. There was no intention of relating these two criteria, and this combination was a technical accident. On the other hand the statistical incidence of this type of headache was not diminished as the result of this combination, as anyone was included who answered either one or the other.

In the headache fraction of the four groups the following percentages were obtained:

TABLE III

	I	II	III	IV (TOTAL)
All 8 criteria	0.0	0.0	0.0	0.0
Any 7 criteria including 1 and 7	0.1	0.0	0.0	0.1
Any 6 criteria including 1 and 7	0.1	0.0	0.2	0.1
Total % of headache fraction	0.2	0.0	0.2	0.2
Total % of entire group	0.1	0.0	0.2	0.1

Therefore we see that Histamine Cephalalgia is a clinical rarity, when rigidly defined.*

*It may be felt by some that sweating of the forehead and face, lacrymation, and unilateral pupillary changes should have been included as criteria for Histamine Cephalalgia. However, the incidence, as surveyed, was already so low, that the inclusion of any additional criteria would have lowered this figure even further. When setting up the original criteria, it was felt that it would be impractical to have more rigid requirements and this was borne out in the incidence determined. Also, it should be stated that the questionnaire had to be kept fairly simple so that satisfactory cooperation could be obtained. In this study, small percentages were not carried any lower than 0.1.

FRONTAL HEADACHE

We were also interested in determining the proportion of headache cases who complained specifically of pain anywhere in the frontal region.[2] The following data were obtained, based on the per cent of the Headache Fraction:

TABLE IV

	I	II	III	IV (TOTAL)
Forehead, one side only	12.4	10.7	13.1	12.3
Forehead, both sides	24.3	44.4	29.0	26.3
Whole front of head	24.0	13.2	22.9	23.1
Eyes	11.4	8.3	9.3	10.9
Total % of headache fraction	72.1	76.6	74.3	72.7
Total % of entire group	47.8	31.3	57.4	47.1

PAIN IN OCCIPITAL REGION OR NECK

It is recognized that pain in the occipital region or neck may exist alone or accompany or follow pain in any other part of the head. Therefore the incidence of this type of pain was determined. Two criteria were used: (1) pain in back of head, and (2) pain in neck. The number of affirmative answers and per cents are reported in the following table.

TABLE V

	I	II	III	IV (TOTAL)
Number answering affirmatively any one criterion	339	40	91	470
Per cent of headache fraction of group	14.2	19.5	21.7	15.6
Per cent of total group	9.4	8.0	16.7	10.1
Number answering affirmatively both criteria	61	11	13	90
Per cent of headache fraction of group	2.6	5.4	4.3	3.0
Per cent of total group	1.7	2.2	3.3	1.9

The percentages of individuals in the above reported categories are graphically demonstrated in Fig. 2.

SUMMARY

In the total number of individuals in the survey (4,634), various types of headaches were found in the following percentages.

Migraine (broadly defined)	8.6
Migraine (rigidly defined)	3.3
Histamine Cephalalgia	0.1
Frontal Headache	47.1
Occipital or neck pain	10.1

Acknowledgment is made of the assistance of Mr. James Villere, Southwest Manager of Sandoz Pharmaceuticals.

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ASTHMA IN CHILDREN

A Review of the Recent Literature

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THE belief by many that children will "outgrow" their allergies is unfortunately still prevalent. Metzger[1] studied the records of 4,000 asthmatic patients to arrive at a very definite answer. He found that, with rare exceptions, every patient had had a remission of his symptoms, that is, the asthma attacks suddenly or gradually disappeared for the time being. Metzger then selected only those cases which had had remissions lasting one year or more. These were then separated into age groups, and the following data were assembled indicating the age at time of remission and the percentage in that age group showing remissions one year or longer: 5 to 10 years—58 per cent; 10 to 20—56 per cent; 20 to 30—61 per cent; 30 to 40—52 per cent; 40 to 50—51 per cent; and 50 to 60—32 per cent. These percentages show that the largest number of remissions occurred in patients 20 to 30 years of age. There seemed to be no apparent difference in the time the remission lasts and the age at which it occurs until the age of 50 is reached. After that age, remissions are not only less numerous, but also definitely shorter in duration.

We are aware that over 5 per cent of the general population suffers from some form of allergy, and that more than 50 per cent of the adults with allergic manifestations will relate a childhood history of allergy. These facts would indicate that allergic disease is not self-limited, but the tendency is for the hypersensitive patient to "outgrow" one allergy and develop another.

The Allergic State in Relation to Prevention and Early Recognition of Asthma

The problem of allergy in the child differs in many respects from that in the adult. Both diagnosis and therapy must be altered in the younger patient to suit the occasion and the condition of the patient. Bigler[2] has stated that anyone practicing pediatrics in this modern day must have a working knowledge and awareness of allergy. The author feels that the prevention of the allergic state is really the initial phase of therapy. Bigler believes that the careful administration of foods to the infant will, in many instances, reveal allergic intolerance that can be recognized, and will permit proper substitution and alteration of diet.

The presence of respiratory allergy in infants is not an uncommon occurrence. In fact, Ratner[3] judges this to be the commonest of all childhood allergic manifestations. He believes that the diagnosis of asthma can be made only upon the basis of repeated attacks of shortness of breath associated with sonorous or sibilant râles, as contrasted with respiratory allergy in adults.

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It has always been of diagnostic importance to ascertain the cause of "wheezing" in infants and children. With this in mind, Schwartzman and Nau[4] have published a study of 151 cases of children admitted to the hospital with "wheezing chest." Of the patients, 88 per cent were under seven years of age, and 58 per cent were under two years of age. The sex incidence was roughly equal. Thirty-nine per cent of the cases were due to allergic causes, and this figure closely paralleled the number of family histories positive for allergic conditions. There were many diverse causes for the wheezing in the remaining 61 per cent, not due to allergy. In most of the patients under two years of age, the tracheobronchial tree was involved directly. Tuberculosis was the etiologic factor in eight cases. There were only two instances of foreign bodies in the bronchi. The authors were of the opinion that nasopharyngeal smears for eosinophils are not as reliable as other writers had appeared to believe. The over-all mortality rate for this series was 6 per cent, a figure which should make one view with alarm a child with a "wheezing chest."

Glaser[5] feels that an incorrect diagnosis of bronchial asthma is perhaps more commonly made in infants and children than in older persons. The two main reasons for this are: (1) congenital stridors are not rare in infants and children, and often produce a wheezing type of respiration; and (2) unsuspected foreign bodies in the bronchi may simulate signs and symptoms of bronchial asthma. The author stresses the importance of chest x-rays in cases of wheezing that are of doubtful origin. If there is still doubt concerning the presence of a foreign body, bronchoscopy is mandatory. It must be remembered that bronchial asthma is only one form of obstructive emphysema, though it is the most common form. Glaser states that the principal differences between signs of bronchial asthma in children and those in adults are: (1) dyspnea in infancy and childhood is not so characteristically expiratory; (2) the asthmatic infant may appear relatively comfortable, even when flat on his back, probably because of the abdominal type of respiration and the greater softness and flexibility of the thoracic cage; (3) absence of an expression of anxiety on the child's part is often in striking contrast to that of the adult.

Nelson and Stoesser[6] concur with Glaser in stating that the onset of bronchial asthma in the young child does not show the same degree of dyspnea as the adult. They also stress that wheezing, with the prolongation of expiration, so common in the adult, is not seen in the same degree in the infant. It is therefore well to keep these differential points in mind so that a diagnosis of asthma in an infant or child may be made before numerous repetitions of symptoms have occurred, or chronic asthma has developed. If the condition is not diagnosed early, serious physical handicaps may develop.

In the differential diagnosis of the asthmatic symptoms in children, Ratner[3] has presented the more common disease entities in pediatrics that may simulate the asthma of childhood. Pertussis is suggested by a predominantly high lymphocyte count in early stages, by absence of allergic history, and by the type of whoop and cough, and is proved by a positive throat spray culture. Cystic fibrosis of the pancreas is diagnosed on the basis of persistence of cough and other signs of disease of the lungs, failure of the patient to gain weight,

and the large, fatty, homogenous, and foul-smelling stools that are typical of this disease. Another cause of intractable cough with asthmatic breathing in infancy may be pressure of tuberculous lymph nodes on the tracheobronchial tree. If every case of uncontrolled dyspnea is diagnosed as status asthmaticus, difficulties will be encountered. The author states that, in the search for the causes of persistent dyspnea simulating asthma in the infant and child, the following conditions must be considered: thymic compression; substernal goiter; adenopathy (most commonly at the bifurcation of the trachea); cicatricial stenosis due to a suppurating mediastinal gland or prolonged sojourn of a foreign body; foreign bodies in air or food passages; subglottic laryngitis; papillomas of the trachea or larynx; pulmonary abscess, bronchiectasis, pneumonia and atelectasis. The importance of a differential diagnosis in uncovering the cause of the asthmatic symptoms in a child is self-evident; the results of specific treatment of bronchial asthma are better in children than in adults, and many of the other conditions producing wheezing dyspnea require prompt therapy.

It is felt by many that the early recognition of allergic symptoms in an infant prior to the onset of asthma will lessen the possibility of a defect in growth and development. Allergic manifestations that may appear prior to the onset of asthma have been presented by Pounders.[7] These various allergic symptoms may be considered the "phases" of pediatric allergy. The author states that the contact between massive and repeated doses of allergenic substances and the cellular antibody of the gastrointestinal tract results in general and segmental enterospasm known as colic. The food may be regularly and forcefully expelled from the stomach; loose bowel movements with passage of mucous and blood may be frequent. Blood- and lymph-borne allergens may react with the sensitized cells of the corium, causing infantile eczema. Unless the condition is understood, and food is properly changed and rotated, the child goes through long periods of illness and discomfort. During the latter part of the first or the second year, or later, the mucosa of the upper respiratory tract begins to take part in the altered reactions. At this time the antigenic substances may be foods and inhalants. Nasal symptoms and frequent "colds" are prominent at this time. Also at this time, or at a future date, the reaction may involve the lower respiratory tract, resulting in attacks of asthma.

It is well then, to consider the symptoms of colic, cyclic vomiting, diarrhea, eczema, coryza, and frequent "colds" in an infant with a positive hereditary allergic factor, as possible precursors of the asthmatic state. Bowen[8] has stressed the relationship that appears to exist between infantile eczema and asthma; 20 per cent of a large group of asthmatic patients stated that they had had infantile eczema, and 50 per cent of a group of eczematous children developed asthma. In obtaining a history, the family background is of great value, 90 per cent of the patients in Bowen's experience having had a positive hereditary factor. Nearly 90 per cent of children with allergic heritage from both parents became asthmatic during the first ten years of life, and about 30 per cent with a heritage from one parent developed symptoms within this period.

Myers[9] has stated that over 90 per cent of allergic persons have their first symptoms before the age of ten. In order of appearance, Myers lists cutaneous manifestations, gastrointestinal symptoms, allergic rhinitis, and asthma. According to the frequency of occurrence, he lists, allergic rhinitis and hay fever, followed by asthma, cutaneous manifestations, and gastrointestinal symptoms.

ETIOLOGIC DIAGNOSIS

Although most allergic children with bronchial asthma show positive reactions on intracutaneous testing with the inhalants, the possibility of infections and foods as etiologic agents must be ruled out by most precise nutritional histories and complete search for foci of infection, especially in the upper respiratory tract area. The relative importance of foods, inhalants, and infection in the etiology of asthma in infants and children has long been a subject of debate. Myers[9] has stated that bronchial asthma in children may be caused by protein sensitivity in 80 per cent of the cases, the agents including pollen, inhalants, foods, bacteria, animal sera, drugs, and molds. "Nonprotein sensitivity" following pneumonia, pertussis, or upper respiratory infection may be the etiological factor in 18 per cent of the cases and tracheobronchial stenosis in 2 per cent.

The statistics of Rowe and Rowe[10] indicate that food is an important factor in the causation of childhood asthma. They reported that food sensitivity was the sole cause of asthma in 50 per cent of 411 children under the age of 5 years. Stoesser,[11] in a study of 329 children with asthma, also found food allergens to be important in infancy and early childhood, while the inhalants were most significant in the latter part of the preschool period. The same opinion has been expressed by Hill[12] who found that 24 per cent of 100 asthmatic children between the ages of three and twelve had asthmatic attacks following the ingestion of certain foods.

Dees[13] performed intracutaneous tests on 100 asthmatic children in an attempt to determine the relative importance of various allergens. The following positive reactions were obtained: dust—83 per cent, pollen—80 per cent, feather—76 per cent, chocolate—38 per cent, milk—37 per cent, cottonseed—36 per cent, wheat—34 per cent, egg—23 per cent, bacteria—86 per cent, and fungi—71 per cent. She found house dust to be the most important allergen, one to which approximately 85 per cent of the patients with respiratory allergy, and many with eczema are skin sensitive. Dees points out that foods are important allergens, although allergists and pediatricians do not agree among themselves as to their relative importance and significance in various clinical allergies. She feels that in dealing with children it is important not to restrict a diet, nor to cast suspicion on foods without excellent reasons, since some mothers and children will use this as a starting point for major food phobias. Dees feels that people become sensitive to the things to which they have repeated, prolonged, and intimate exposure, and our food sensitivities reflect very closely our eating habits. We feel that it is probably safe to say that foods as etiologic factors are less important in childhood respiratory allergy than are the air-borne allergens.

Ratner[3] noted that, although it has been thought that food sensitivities play the dominant role in allergy in childhood, sensitivities to foods, inhalants, and contactants, run a more or less parallel course. The trend in recent literature reviewed would indicate a more conservative attitude toward the importance of food as an etiologic factor in asthma.

There appears to be general agreement as to the frequency of sensitization to the various allergens concerned in the causation of inhalant respiratory allergy. The pollens, fungi, house dust, animal danders, and others are commonly recognized as causes of asthma in childhood.

Infection as a factor in the cause of bronchial asthma in children has been the subject of much controversy in recent reports. The occurrence of infective asthma in infants and children is still unrecognized by many leading allergists, while others consider this one of the main etiologic types. Chobot, Uvitsky, and Dundy,[14] in an attempt to indicate the relative importance of infection in childhood asthma, studied 400 children whose asthma began before they were three years of age. They analyzed their cases and divided them into two groups: (1) those having a single etiologic factor, i.e., infection, inhalant, or food, and (2) those with a combination of two or all three of these factors. The assembled data are shown in Table I.

TABLE I. CAUSES OF ASTHMA IN 400 INFANTS AND CHILDREN WHOSE ASTHMA BEGAN BEFORE AGE OF 3 YEARS

FACTORS	PER CENT
Sole Factors	
Infection	30.50
Inhalant	10.25
Food	0.25
Total	41.00
Combined Factors	
Infection, inhalant	44.25
Infection, food	4.75
Infection, inhalant, food	7.75
Inhalant, food	2.25
Total	59.00
All cases with infective factor	87.25
All cases with inhalant factor	64.5
All cases with food factor	15.0

These figures would indicate that infection is one of the most important causes of asthma in infants and children with foods playing a subordinate role and inhalants less important than previously considered in asthma of infants. Chobot emphasizes the fact that infective asthma exists in infancy, and is one of the most important clinical manifestations of bacterial allergy. Chobot states that chronic focal infection must be recognized as a cause of asthma, and therapy directed toward its control.

Feingold[15] feels that infection plays a dual role in allergy. First, it may participate in tissue hypersensitivity of the fixed tissue variety; and second, it may influence the course of an existing allergy. When infection influences the course of an existing allergy, it produces one of two patterns depending upon the nature of the infection. With the acute infectious diseases, pertussis,

measles, mumps, chicken pox, roseola infantum, Kaposi's disease, and the epidemic viral infections, allergic symptoms are usually improved at the peak of the infection. He also states that upper respiratory infections and chronic infections tend to aggravate allergy at the peak of the infection. The author therefore feels that management of allergy with chronic infection usually necessitates removing the foci of infection and good treatment for the allergy that exists.

The role of bacterial products in the various types of allergy has recently been stated by Cooke[16] who feels that while the bacterial products may be the antigens, they also act as synergists, or adjuvants, in the production of antibodies, even to homologous cells. Typical anaphylactic reactions can be produced with bacterial proteins in animals. Many different types and strains of bacteria produce typical signs and symptoms of asthma where the shock organ comprises components of the bronchial tree. This statement is substantiated by production of asthmatic symptoms with minimal subcutaneous doses of a suitable bacterial suspension; the pathologic picture of fibrinoid degeneration of tissue and eosinophilia in the bronchial walls and blood tends to support this hypothesis of allergy. Cooke further states that all patients with asthma should be studied carefully for areas of focal infection soon after the asthma occurs. Search for focal infection should be made in younger patients with seasonal or perennial coryza from any cause, and allergically predisposed children with frequently recurring bronchitis, whether there is asthma or not.

THERAPY TO INFECTIVE ASTHMA

The most common source of focal infection in children is within the lymphatic tissue of the nasopharynx; mainly, the tissue involved is that of the tonsils and adenoids. The question of tonsillectomy in the allergic child brings forth advice by Bowen[8] who feels that more conservatism is recommended with reference to tonsils and adenoids in asthmatic children. He feels that the lymphoid tissue is frequently hypertrophic, and that there is a marked tendency to its recurrence after removal. Clein,[17] who has also been concerned with the tonsil problem in children, found that, in practically all instances where the tonsil and adenoid tissue recurred, an allergic basis for the original symptoms had not been recognized preoperatively. Bigler[2] and others believe that the tonsil question can best be answered by using the same criteria for removal in both the allergic and nonallergic child. We are of the opinion that the complete surgical removal of all infected tissue is the first step in the intelligent approach to the treatment of infective asthma in childhood. At the same time, one must keep in mind that edema is a factor in enlargement of tonsils in allergic children; and, as Feingold[18] has stressed, with this edema, a large, pale, boggy, and succulent tonsil results. This type of tonsil, when coupled with symptoms of allergic reaction—nasal itching, sneezing, rhinorrhea, post-nasal drip, and cough—gives a clinical picture often mistaken for recurrent upper respiratory infection. Since this is an expression of the influence of allergy on the lymphatic structures, surgical removal of the tonsils or adenoids, in absence of infection, will not alleviate the symptoms. Only

thorough management of the allergic diseases can offer control in this type of case. The indiscriminate removal of lymphoid tissue may result in both physical and emotional harm to the young allergic patient.

Lederer and Grossman[19] have emphasized that the tonsil is now known to be a useful organ, especially in the younger child, in whom it plays a major role in autovaccination and as a body defense mechanism. They also, as otolaryngologists, condemn the removal of large, uninfected tonsils for prophylactic reasons, as valueless and detrimental. It is generally agreed that a tonsillectomy should command all the respect due a major operation, and should be performed only by well-trained otolaryngologists who are familiar with the problem. Moreover, if the operation is not meticulously and completely performed, tonsillar remnants are often left, which may be more harmful than the original tonsil.

Since it is impossible to eradicate completely the infected nasopharyngeal lymphoid tissue by surgery, because lymphoid tissue is an integral part of the mucous membrane of the nasopharynx, and since this lymphoid tissue is exceedingly susceptible to hyperplasia under the stimulus of infection and allergy, the irradiation procedures advocated by Crowe and Ward[20] appear to have a definite place in the treatment of infective asthma. Cohen and Fisher[21] treated fifteen children, aged 4 to 16, with perennial asthma. Each had positive skin reactions to various allergens. All but two had had tonsillectomies. Treatment consisted of 6½ minutes' exposure to 100 mg. radium contained in the Crowe applicator applied to the nasopharynx. Four treatments were given at intervals of 21 days. In most cases improvement in asthmatic symptoms was obtained for about seventeen weeks following radium treatment. An attempt was made to determine whether asthmatic children who showed signs of infection as demonstrated by the sedimentation rate responded better than those without signs of infection. The sedimentation rate was chosen for this purpose as it was considered to be the most sensitive indication of infection. In general, children with elevated sedimentation rates who received radium treatments to the nasopharynx were benefited for longer periods than those with normal rates. The amount of adenoid tissue in the nasopharynx of each patient was estimated from a lateral x-ray plate of the nasopharynx. The patients were then classified from 0 to 4 plus. Patients having the least amount of adenoid tissue in the nasopharynx obtained more relief than those having greater amounts. It was also noted that children with normal sinuses obtained better relief from the asthma after radium therapy than patients with hyperplastic sinusitis. The authors concluded that, on the whole, the beneficial response obtained directly following the course of radium therapy is very similar to results obtained in patients treated with nonspecific therapy. However, the better response to radium therapy in patients with high sedimentation rates seems to indicate that chronic infection in the nasopharynx is benefited by this treatment.

Spain and Weymuller[22] have reported the irradiation procedures of Crowe and Ward[20] as being found successful in the great majority of asthmatic children with residual infected lymphatic tissue in the nasopharynx, as evident by

direct visualization with the nasopharyngoscope and lateral x-rays of the nasopharynx. Of the forty-four children ranging from 1 to 16 years of age, upon whom full data could be obtained, nine cases (or 20 per cent) obtained complete relief following irradiation therapy, twenty-five cases (57 per cent) obtained partial relief, and ten cases (23 per cent) unsatisfactory relief. The cases obtaining complete relief reported no asthmatic episodes with few or no acute upper respiratory infections in the period of six months or longer since the last radium therapy, a period which always included the preceding winter. This result was in contrast with the occurrence, before treatment, of repeated head colds and asthma one or more times monthly. The authors therefore conclude that, in experienced hands, and upon selected cases, irradiation therapy offers a safe and effective means of combating infective asthma in childhood.

In conjunction with the surgical removal of the foci of infection and the use of radiation therapy, the use of the various antimicrobial agents has been of inestimable value in the treatment of infective asthma. Aerosols of the antibiotics have proved of real value in combating infections, especially those associated with the lower respiratory tract.

General reactions following the treatment of asthma in children with bacterial vaccines have been reported by Flensborg.[23] He noted general reactions of varying degree in 42 of 162 asthmatic children treated with stock-mixed, respiratory bacterial vaccine. Reactions were usually of the delayed type, occurring about 48 hours after the injection, and lasting from 6 hours to 6 days. Repeated overdosage, even if it only results in slight reactions, the author feels, may induce a status asthmaticus, or a prolonged rise in temperature. A fatal reaction attributed to an injection of vaccine was observed in a 1-year-old child. The author suggests that small dosages of vaccine should be used and that close attention should be paid to even slight reactions. He states that temperature readings taken during the first four days following injections often afford valuable information as to proper dosage.

Because of the remarkable results obtained in the prevention of rheumatic fever, and of the greatly reduced incidence of upper respiratory infections, particularly by the streptococcus, pneumococcus, and meningococcus, with sulfonamides, attempts have been made to use these drugs in the prevention of infective asthma. Fishman[24] treated 20 patients who suffered from regularly recurring infectious asthma and/or bronchitis and who failed to respond to allergic or other treatment, with sulfonamide prophylaxis for a period of 7 to 9 months. He gave 1.0 Gm. of a mixture of equal parts of sulfadiazine and sulfamerazine, daily in two doses to patients weighing over 100 pounds. Only 0.5 Gm. daily was given to those patients weighing under 100 pounds. This treatment was usually started in October, and the dose was cut to 0.5 Gm. daily after April and continued to June. With this type of therapy, no severe attacks of asthma or bronchitis occurred in any who took the prophylactic treatment faithfully. Three patients who stopped the sulfonamides for several weeks experienced a recurrence of their asthma following an acute respiratory infection. The others, who took sulfonamide medication continuously, had no serious recurrences even after an acute respiratory infection. Only one general

reaction occurred—a skin eruption appearing in a patient who was sensitive to other drugs. Fishman recommends this method of prophylaxis for the prevention of infectious asthma in those children who have recurrent attacks of asthma caused by respiratory infection for whom other methods of treatment have failed. Allergic and other medical management should be continued during sulfonamide prophylaxis.

SYMPTOMATIC THERAPY

A comprehensive pharmacologic analysis of the drugs used in allergy recently, compiled by Leake,[25] clearly states the need for careful judgment in the choice of the correct drug in the treatment of asthmatic children. Since many children with asthma unfortunately suffer from overtreatment, it is important to avoid disturbing one function in the treatment of another. Leake classified the allergic drugs as follows.

1. General cellular stabilizers which may aid in preventing allergy. They include protein in adequate amounts for proper globulin synthesis of antibodies, and various vitamins and minerals, especially ascorbic acid, carotenoids, and calcium which bind the cells together and preserve cell membrane permeability.

2. Chemotherapeutic and antibiotic agents which are effective in controlling low-grade infections.

3. Antipyretic analgesics reverse cellular inbibition of water in allergic processes, thus giving relief from pain due to congestion and associated malaise.

4. Smooth muscle relaxants, such as aminophylline and papavarine, may give some symptomatic relief from spasm of the bronchial musculature which has been caused by the imbibition of water.

5. Sympathomimetic smooth muscle relaxants, such as epinephrine, ephedrine, and benzedrine give symptomatic relief from smooth muscle spasm.

6. Antihistaminics, in general, block the action of histamine.

The antihistaminics have contributed much to the symptomatic relief of allergic states characterized by pruritis, localized edema, and urticaria, but they have not been of much value in the relief of asthma or the more severe cutaneous and gastrointestinal forms of allergy. Stoesser[26] has given a clinical appraisal of the antihistamine drugs in a study of 4,714 cases seen in two hospital allergy clinics and in private practice. The antihistamines, as they became available over the past five years, were studied in children aged 6 months to 16 years, all with allergic manifestations. Fifteen drugs were given in rotation under controlled conditions of diet and environment, over periods to include all seasons. No specific immunization procedures were used during the study. Doses ranged from one-fourth to twice the recommended amount, beginning with small amounts and increasing the tolerance to observe side effects and discover if large amounts offered more relief than smaller quantities.

Clinically, beneficial responses were obtained with all the drugs; the percentage of satisfactory results was 48. There were 153 children who could not take the drugs, leaving 4,561 cases distributed as shown in Table II.

TABLE II. RESPONSE OF VARIOUS ALLERGIC DISEASES TO 15 ANTIHISTAMINICS

DISEASE	CASES	SATISFACTORY RESULTS	
Atopic eczema	255	71	28%
Allergic rhinitis	2,436	1,632	67%
Hay fever	964	511	53%
Asthma	526	95	18%
Urticaria-angioedema	204	179	88%
Gastrointestinal allergy	31	13	42%
Migraine	71	22	31%
Conjunctivitis	74	42	57%

There has appeared in recent literature a widespread interest in the use of the various sympathomimetic aerosols for the management of bronchial asthma. Segal and associates[27] made a comparative study of three sympathomimetic amine aerosols in common use: epinephrine hydrochloride 1:100 U.S.P., Vaponephrin (a 2.25 per cent solution as specially prepared recemic epinephrine hydrochloride), and Isuprel (1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol) hydrochloride in a 1:200 dilution. To determine the relative efficiency of these various aerosols as antihistaminic or anticholinergic agents, they measured in the laboratory the ability of these substances to prevent the occurrence of the dyspnea and bronchospasm which follows the intravenous administration of histamine and of acetyl-beta-methylcholine to sensitive asthmatic patients whose age groups were not mentioned. It was concluded by the authors that both Isuprel 1:200 and Vaponephrin have valuable places in the armamentarium of the allergist. Krasno et al[28] treated twenty-four patients with bronchial asthma by means of Norisodrine dust inhalation. (This drug is chemically identified as 1-(3,4,-di-hydroxphenyl)-2-isopropylaminoethanol, and has been known in the European literature as Aleudrine.) Nineteen responded satisfactorily, and were under complete control with this form of therapy. Four showed a good response, and one patient was not influenced at all. Sixteen patients were controlled by the inhalation of the Norisodrine sulfate as a dust only; eight required Norisodrine plus aminophylline and iodides, and/or an antihistaminic. The combination of drugs has been found by the authors, to be effective where each drug, by itself, is not effective.

Another new addition to the group of sympathomimetic compounds, Orthoxine (orthomethoxy-beta-phenyl-isopropyl methylamine hydrochloride), has been studied by Curry, Fuchs, and Leard.[29] Clinical studies of Orthoxine and ephedrine sulfate were made in two groups of patients with bronchial asthma. Experiments indicated that Orthoxine has a definite place in the treatment and management of bronchial asthma, since it is an effective bronchodilator drug, which may be given orally, and is followed by relatively few undesirable side reactions.

A very interesting publication by Black and Holman[30] concerning the use of dust extract by mouth in the treatment of respiratory allergy in children is worthy of note. These authors began to use house dust as an antigen in the treatment of house dust-sensitive children, all of these patients being under the age of thirteen. It was felt that dust or pollen in each of these patients was a definite and primary etiologic factor in the production of their respiratory

allergy. Dust therapy by mouth was carried out with the same concentrated glycero-saline extract as that used for hypodermic therapy. Oral therapy was given to 402 children. Of these, 73 were considered to be only dust sensitive, and eventual results showed 67 of these to be classified as obtaining good results. The dust-sensitive patients showed better results by far than did the pollen-sensitive patients on oral therapy. However, hypodermic therapy gave satisfactory relief in a large number of these patients who did not obtain relief by the oral method.

With the introduction of the steroid hormones, ACTH and cortisone, the medical literature has been filled with reports of the uses and dangers of these drugs. Sufficient time has now elapsed to permit a more complete over-all evaluation of the clinical usefulness of ACTH and cortisone.[31] Their effect on status asthmaticus is without doubt dramatic in the majority of cases; but clinical experience has now shown that the relief offered by these hormones is temporary and not curative, the asthma recurring after discontinuance of medication. Infants and children react to these hormones essentially as do adults, except that they require larger doses in proportion to their body weight. The dose of the drug, within limits yet to be determined, depends upon the age or weight of the child. ACTH and cortisone do not interfere with the results of the immediate wheal type of reaction as commonly employed in skin testing with the customary allergens. It is therefore possible to relieve the patient in status asthmaticus and then proceed with skin testing procedures without undue suffering on the part of the patient.

Glaser et al.,[32] treated a series of 13 children, ranging in age from 18 months to 15 years, suffering principally from eczema, and 10 from bronchial asthma. Both hormones were found to be potent agents in the temporary relief of bronchial asthma in infancy and childhood. The longest remission in this series of asthmatic children occurred in a 9-year-old boy who remained symptom-free for a period of four months after stopping ACTH therapy. It is the opinion of these authors and other investigators that, in the present state of our knowledge, we must recognize that these drugs possess great potential for harm, as well as good, and should be used in cases of intractable status asthmaticus to "tide" the patient over the severe episode only when all other therapeutic agents fail.

Since it is fairly well accepted that the wheezing in asthma is effected by air passing through partially obstructed bronchi, and that this obstruction is caused by mucus as bronchospasm, Waldbott[33] has strongly advocated the use of bronchoscopy as a means of therapy in allergic asthma. The author reviewed the results of 180 bronchoscopies on 127 patients. In this series, bronchoscopy was performed: (1) to prevent a moribund patient from becoming asphyxiated through the accumulation of mucus; (2) to break up a chronic asthmatic state; (3) to remove a single mucous plug which had caused atelectasis; (4) to dilate bronchial strictures; and (5) to remove mucus from bronchiectatic areas.

Eight patients were refractory to all medications and were moribund. In all but one patient, asthma subsided after 30 to 60 c.c. of thick, pasty ma-

terial was removed through aspiration and lavage with saline solution. Status asthmaticus was the indication for bronchoscopy in 119 patients. Complete relief occurred after a single treatment in nine patients. Considerable improvement occurred in 53 additional patients after one or more bronchoscopic treatments. Three of four patients with stricture of bronchi showed complete and dramatic recovery from long-standing asthma after a single bronchoscopic dilatation. Stricture of the bronchi may be confused with allergic asthma, and hence must be differentiated. Stricture is characterized by exceedingly chronic and persistent wheezing, nonproductive cough, suppression of breath sounds and fremitus over the area, and episodes of fever due to localized pneumonitis. Waldbott feels there is no need for bronchoscopy when there is little or no mucous secretion, or the sputum is thin and watery, and is contraindicated under these conditions. This is true in asthma of short duration with edema of the alveoli associated with, or followed by, pneumonitis, in incipient asthma characterized by a nonproductive pertussis-like bronchitis, in sudden, severe attacks of asthma after injection, ingestion, or inhalation of antigens, and in asthmatic attacks of psychsomatic origin.

COMPLICATIONS

The complications of bronchial asthma are not as prominent in children as they are in adults. A common complication seen in children, reversible bronchiectasis, has received comment in recent pediatric writings, indicating its importance as a possible end result of childhood asthma, if the condition is not properly managed. Freed[34] studied 160 children ranging in age from one to twelve years. All of these patients had irreversible bronchiectasis. In 55 per cent of these patients, pneumonia was associated with the onset of symptoms, or the initiation of symptoms was subsequent to an attack of pertussis. Asthmatic symptoms were noted in 33 per cent of the children studied. Bronchography was the most important single procedure used in making a diagnosis in this series.

Freed[34] studied 99 children with doubtful bronchiectasis, and found that almost half had asthma which was often difficult to distinguish from the irreversible bronchiectasis, even after bronchograms. He also noted that, after three or more years, 40 of the 99 had developed true irreversible bronchiectasis, proved by bronchography. On the other hand, Waldbott and associates,[35] feel that irreversible bronchiectasis is very rare in bronchial asthma if it does exist at all in association with this allergic disease. They have suggested the term "pseudobronchiectasis," thus setting it off as a benign, reversible process upon an allergic background for which surgery is not indicated.

Interstitial mediastinal emphysema complicating asthma is extremely rare in children as it is in adults. Of the seventy-three cases of spontaneous mediastinal emphysema reported in the literature, only 28 were due to asthma. Kahn and Rouse[36] have recently reported this complication in a 5-year-old boy, and have offered a possible explanation of the sequence of pathologic changes that may have taken place in this case.

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Editorial

THE FOUNDATION FOR THE ALLERGIC DISEASES

The importance of allergic diseases as causes of disability is familiar to all physicians. The United States Public Health Service has estimated that in 1948 there were 3,900,000 persons in this country suffering from asthma and hay fever, these two allergic diseases ranking third in prevalence among types of chronic disase exceeded only by heart and circulatory diseases and arthritis and rheumatism. In England and Wales, Dr. D. A. Williams of Cardiff found that asthma alone caused more disability than hypertension and heart disease and almost twice as much as all forms of tuberculosis.

Despite the amount of disability they cause, the allergic diseases have received relatively little attention in the development of specialized facilities for treatment, in research and in medical education. Even in cities with the best of general hospitals, it is often difficult or impossible for the asthmatic patient of modest means to obtain adequate care. Severe asthma requires the most intense medical and nursing service, yet many acute cases persist far longer than the acute stage of most other diseases. As a result, hospitals treating acute diseases are often reluctant to admit such patients and institutions offering chronic care are poorly equipped to handle them. Too often, the hospital treatment of asthma consists merely of temporary relief of symptoms without an adequate investigation of the cause or a plan for prevention of recurrence. Changes of environment which may be advisable in order to avoid pollen antigens, respiratory infections or other causative factors are usually feasible only for the wealthy, and special drugs such as cortisone may be prohibitively expensive if needed for a prolonged period.

While notable advances have been made in the study of mechanisms and therapy of allergic diseases, research in this field has lagged far behind that in other branches of medicine; for example, cardiology. Few able investigators have devoted their full time to studies in this field of medical science. The bulk of the research has been done by busy practitioners often with meager training in the basic sciences aided by residents or fellows whose primary interest is also in clinical rather than investigative medicine. Financial support of research has been uncertain, usually dependent upon sporadic donations from philanthropists or drug manufacturers with whom the investigator has personal contacts. The increasing complexity of research methods is leaving both the personnel and the financial support inadequate. Furthermore, facilities for teaching allergy to medical students, interns, and residents have been poorly developed, so that the subject has not attracted much interest among the younger graduates and relatively few well-trained young specialists are entering the field.

To extend our present knowledge of allergy, to apply the best methods to the treatment of patients of limited financial resources, and to train young physicians adequately to carry on this work, will require both money and arousing the interest of the public, the medical profession, and medical students. In many fields of medicine this has been accomplished by large national foundations combining outstanding medical and lay leadership with professional aid in publicity and fund-raising, such as the American Cancer Society, the American Heart Association, and the National Foundation for Poliomyelitis. Even in such relatively limited fields as multiple sclerosis and cerebral palsy, similar organizations have aroused public interest and support. If the same type of work is to be done in allergy a comparable organization is needed.

At the Chicago meeting of the American Academy of Allergy, plans were laid for a Foundation for the Allergic Diseases, to carry out these functions on a national scale. A board of medical trustees has been established, and immediate plans call for engaging the services of a public relations firm to survey the prospects of arousing public support.

Such a plan offers great possibilities of promoting the study and practice of allergy. In view of the prevalence of allergic diseases and the existing public interest, it has an excellent prospect of success if properly handled and supported by the medical profession. Once established the Foundation will function independently of the Academy, and have the backing of all physicians working in allergy. With this in mind, the medical trustees have been chosen to include outstanding members of the American College of Allergists as well as of the Academy. However, the desired unity of action can result only if they function as individual representatives of the medical profession rather than as delegates from either of the existing allergy societies.

The proposed Foundation deserves the good will and support of all who suffer from or treat allergic diseases. The present group of medical trustees inspires confidence that it will accomplish its purpose.

American Academy of Allergy

The following were elected to membership in the American Academy of Allergy at the Eighth Annual Meeting in Chicago, February, 1952.

Honorary Fellowship

Merrill Chase, Ph.D.
Bernard N. Halpern, M.D.
Charles W. Loeffler, M.D.
Ernst Salen, M.D.

Emeritus Fellowship

Arthur F. Roche, M.D.
Jack A. Rudolph, M.D.
Alexander Sterling, M.D.

Advancement to Fellowship

Ethan Allan Brown, M.D.
Paul E. Carliner, M.D.
Francis E. Chafee, M.D.
Paulo Dias da Costa, M.D.
Benjamin F. Feingold, M.D.
Henry T. Friedman, M.D.
L. Dell Henry, M.D.
Frank T. Joyce, M.D.
Cecil H. Kohn, M.D.
S. Walter Landau, M.D.
A. M. Marchand, M.D.
Howard S. Mitchell, M.D.
Dean A. Moffat, M.D.
Louis Noun, M.D.
John W. Parsons, M.D.
Frank F. A. Rawling, M.D.
George J. Seibold, M.D.
Ramon Surinyach, M.D.
Albert M. Tocker, M.D.
John H. Trescher, M.D.
Irving H. Uvitsky, M.D.

Direct Election to Fellowship

Egon Bruun, M.D.
Umberto Serafini, M.D.

Affiliate Fellowship

Elmer L. Becker, M.D.
H. G. D. Breidahl, M.D.
C. M. Christensen, Ph.D.
Ralph F. Voigt, Ph.D.

Emeritus Membership

Herman N. Eisen, M.D.

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Louise Kappes, M.D.
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John J. McKenna, M.D.
Nadhim E. Meer, M.D.
Harry L. Mueller, M.D.
Plutarco Naranjo, M.D.

Henrietta D. Necheles, M.D.
George J. Piazza, M.D.
Edward Pickert, M.D.
Carroll N. Pounders, M.D.
Charles E. Reed, M.D.
Michael Schwartz, M.D.
Roland B. Scott, M.D.
Arthur H. Sussman, M.D.
Hugh G. Thompson, M.D.
Charles W. Vivian, M.D.
Aaron Weiner, M.D.
Richard Wiseman, M.D.

EXTRACT FROM THE REPORT OF THE COMMITTEE ON THERAPY OF THE AMERICAN ACADEMY OF ALLERGY

CARL E. ARBESMAN, M.D., CHAIRMAN

Further reports from five committee members on the use of Allergex for control of dust sensitivity were received. It is the consensus of these members that the dust factor is definitely reduced by the use of this substance. No reports of damage to fabrics, furniture, or rugs were reported. It is suggested that this substance could be recommended as adjunct, but not substitute therapy in the treatment of the dust sensitive case.

Announcement

The Danish Society for Allergological Research

has the honour to announce that the

SECOND EUROPEAN CONGRESS OF ALLERGY

according to the proposal given to the Northern countries in Paris, 1950, will be held in Copenhagen on the 21st to the 23rd of May, 1953, under the presidency of Dr. Ernst B. Salén, Stockholm.

The subjects proposed for discussion are:

(1) Allergy and Adrenal Hormones
(2) Allergy and Infection.

A detailed program and the names of the reporters will be published in due course.

Pan-American physicians are cordially invited to attend and participate in the discussions.

For further information please apply to the secretary-general, Dr. Egon Bruun, Gersonsvej 8, Hellerup, Copenhagen, Denmark.

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Vol. 23, No. 6, November, 1952. The Journal of Allergy is published Bi-Monthly by the C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $8.50; in Canada and other foreign countries, $9.00. Entered as second-Class Matter, November 15, 1929, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in the U. S. A.

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